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Potentiation of the discriminative-stimulus effects of methamphetamine by the histamine H_3 receptor antagonist thioperamide in rats

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Abstract

In order to assess the role of histamine H_3 receptors in the discriminative-stimulus effects of methamphetamine, rats were trained to discriminate 1.0 mg/kg methamphetamine, i.p., from saline under a fixed-ratio schedule of food presentation. The histamine H_3 receptor antagonist thioperamide (1.0 mg/kg s.c.), which facilitates histamine release, significantly shifted the methamphetamine dose–response curve to the left when tested together with different doses of methamphetamine and markedly extended the time-course of methamphetamine's discriminative-stimulus effects. The histamine H_3 receptor agonist *R*-α-methylhistamine (3.0 mg/kg i.p.), which blocks histamine release, did not produce any effects when given alone, but it attenuated the effects of thioperamide on the methamphetamine dose–response curve when both drugs were given together. Thus, methamphetamine's discriminative-stimulus effects are markedly potentiated by the blockade of histamine H_3 receptors by thioperamide. This is likely due to thioperamide's actions at histamine H_3 autoreceptors on histaminergic neurons to facilitate release of histamine by methamphetamine or at histamine H_3 heteroreceptors on other monoaminergic neurons (e.g., dopaminergic, serotonergic or noradrenergic) to facilitate release of other neurotransmitters.

Keywords: Methamphetamine; Histamine H_3 receptor; Thioperamide; *R*-α-methylhistamine; Drug-discrimination; (Rat)

1. Introduction

Methamphetamine is a frequently abused amphetamine derivative with pronounced psychomotor stimulant actions that appear to be related to the release of dopamine, norepinephrine and serotonin (Kuczenski et al., 1995; Sasaki et al., 1995; Munzar et al., 1998a,b; Tidey and Bergman, 1998). Recent findings suggest that histamine release by methamphetamine may also contribute to its actions (Clapham and Kilpatrick, 1994; Ito et al., 1996b, 1997a). Methamphetamine induces histamine release in different brain regions both in vitro and in vivo (Ito et al., 1996a,b, 1997b) and after chronic methamphetamine administration, there are changes in brain histamine receptor levels (Kubota et al., 1998). Histaminergic agents can also modulate methamphetamine-induced stereotyped behavior and behavioral sensitization to methamphetamine (Ito et al., 1997a). There have been some reports that histamine H_1 receptor antagonists can produce amphetamine or methamphetamine-like discriminative-stimulus effects (Evans and Johanson, 1989; Yasar et al., 1992; Suzuki et al., 1996, 1997), but the role of histamine in these actions of histamine H_1 receptor antagonists is not clear.

Endogenous brain release of histamine is regulated predominantly by histamine H_3 autoreceptors that are involved in the feedback control of histamine synthesis and release (Arrang et al., 1987; Schwartz et al., 1991). Their stimulation by the selective histamine H_3 receptor agonist *R*-α-methylhistamine (Fig. 1) inhibits brain histamine synthesis and release, whereas their blockade by the selective histamine H_3 antagonist thioperamide (Fig. 1) may increase brain histamine release (Oishi et al., 1989). Moreover, stimulation or blockade of histamine H_3 heteroreceptors, which are located on non-histaminergic neurons, may

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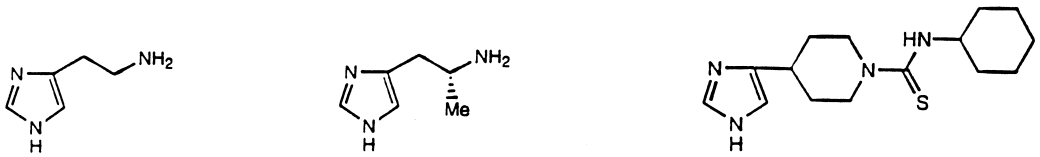

Fig. 1. Chemical structures of histamine, *R*-α-methylhistamine and thioperamide.

also influence dopaminergic (Schlicker et al., 1993; Fleckenstein et al., 1994), serotonergic (Fink et al., 1990) and noradrenergic (Timm et al., 1998) neurotransmitter activity. Although modulation of methamphetamine's or amphetamine's discriminative-stimulus effects by histamine H_3 receptor agents has not yet been described, attenuation of amphetamine-induced locomotor activity by thioperamide has been reported (Clapham and Kilpatrick, 1994).

The present experiment was designed to investigate involvement of histamine H_3 receptors in the discriminative-stimulus effects of methamphetamine. If histamine release were involved in methamphetamine's discriminative-stimulus effects, *R*-α-methylhistamine and thioperamide would be expected to modulate these effects. In order to test this possibility, rats were trained to discriminate methamphetamine from saline. Subsequently, the ability of *R*-α-methylhistamine and thioperamide either to attenuate or to facilitate methamphetamine's discriminative-stimulus effects was investigated.

2. Material and methods

2.1. Subjects

A total of 10 male Sprague–Dawley rats (Charles River, Wilmington, MA) initially weighing 280 to 350 g were housed individually. Their body weights were gradually reduced to approximately 80% of free feeding by limiting daily access to food. Water was available ad libitum. All rats were housed in a temperature- and humidity-controlled room and were maintained on a 12 h light/dark cycle—the lights were on from 6:45 AM to 6:45 PM. Experiments were conducted during the light phase.

Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals (National Research Council, 1996).

2.2. Apparatus

A total of 10 standard operant chambers (Coulbourn Instruments, Lehigh Valley, PA) were used. Each chamber contained two levers, separated by a recessed tray into which a pellet dispenser could deliver 45 mg food pellets (F0021, Bioserv, Frenchtown, NJ). Each press of a lever with force of 0.4 N through 1 mm was recorded as a response and was accompanied by an audible click. The operant chambers were controlled by microcomputers using the MED Associates MED-PC software package (MED Associates, East Fairfield, VT).

2.3. Drug discrimination training

Rats were trained as described previously (Munzar et al., 1998a; Yasar et al., 1993) under a discrete-trial schedule of food-pellet delivery to respond on one lever after an injection of a training dose of 1.0 mg/kg of methamphetamine and on the other lever after an injection of 1.0 ml/kg of saline vehicle. For half the rats, the right lever was the drug lever and for the other half, the left lever was the drug lever. Injections of methamphetamine or saline were given i.p. 15 min before the start of the session. At the start of the session, a white house light was turned on and in its presence the rats were required to make 10 consecutive responses (fixed-ratio 10 schedule of food delivery; FR10) on the lever appropriate to the presession treatment (1.0 mg/kg methamphetamine or saline). The completion of 10 consecutive responses on the correct lever produced delivery of a 45 mg food pellet and initiated a 45-s time-out during which lever-pressing responses had no programmed consequences and the chamber was dark. Responses on the incorrect lever had no programmed consequences other than to reset the FR requirement on the correct lever. After each time-out, the white house light was again turned on and the next trial began. Each session ended after completion of 20 trials or after 30 min elapsed, whichever occurred first.

Discrimination-training sessions were conducted 5 days per week under a double alternation schedule (i.e., DDSS-DDSS, etc., D = drug (methamphetamine), S = saline). Training continued until there were eight consecutive sessions during which rats completed at least 90% of their responses during the session on the correct lever and no more than four responses occurred on the incorrect lever during the first trial. Once this level of performance was maintained for at least eight consecutive sessions, test sessions with other doses and other drugs were then initiated.

2.4. Drug discrimination testing

Test sessions were identical to training sessions with the exception that 10 consecutive responses on either lever ended the trial. In a test phase, a single alternation schedule was introduced and test sessions were usually conducted on Tuesdays and Fridays. Thus, a 2 week sequence starting on Monday was: DTSDTSTDST (T = test). In this way, test sessions occurred with equal probability after saline and drug conditions. Test sessions were conducted only if the criterion of 90% accuracy and not more than four incorrect responses during the first trial was maintained in the two preceding training sessions.

During test sessions, a range of doses of thioperamide or *R*-α-methylhistamine were either substituted for the 1.0 mg/kg training dose of methamphetamine or were given together with the 1.0 mg/kg training dose of methamphetamine. After testing a range of doses of thioperamide and *R*-α-methylhistamine, the effects of selected doses of the two compounds separately, and in combination on the methamphetamine dose–response curve were established.

Subsequently, the effects of selected doses of thioperamide and *R*-α-methylhistamine on the time-course of the discriminative-stimulus effects of methamphetamine were measured. During time-course experiments, 10 min after pretreatment with either saline, thioperamide or *R*-α-methylhistamine, either the 1.0 mg/kg training dose of methamphetamine or a 0.3 mg/kg dose of methamphetamine were injected and after an additional 15, 30, 60, 120, 180 or 240 min the test session started.

2.5. Drugs

Methamphetamine HCL (D-methylamphetamine) was purchased from Sigma (Sigma, St. Louis, MO), thioperamide maleate from RBI (Research Biochemicals International, Natick, MA) and R(−)-α-methylhistamine 2HBR from Tocris Cookson (Tocris Cookson, Ballwin, MO). Doses of all drugs refer to the salt. Drugs were dissolved in 0.9% NaCl and injected either i.p. (methamphetamine and *R*-α-methylhistamine) or s.c. (thioperamide) in a volume of 1.0 ml/kg. Methamphetamine, thioperamide and *R*-α-methylhistamine were injected 15 min before the session in the substitution tests. In combination tests, thioperamide and *R*-α-methylhistamine were injected 25 min before the session and methamphetamine was then injected 15 min before the session. During time-course experiments, different pretreatment times were used as mentioned above. A range of doses of each drug was tested and dose was increased until the tested drug in combination with methamphetamine produced suppression of response rate.

2.6. Data analysis

Results were expressed as the percentage of the total responses on both levers that were made on the methamphetamine-appropriate lever. Complete generalization to the methamphetamine-training stimulus was defined as 90% or more of responses on the methamphetamine-appropriate lever, while no generalization was defined as less than 10% of responses on the methamphetamine-appropriate lever. Response-rate data were expressed as responses per second averaged over the session, with responding during time-outs not included in calculations. All results are presented as group means (±S.E.M.).

Statistical analysis was done by using one-way analysis of variance (ANOVA) for repeated measures. Significant main effects were analyzed further by subsequent paired comparisons using Dunnett's test. Changes were considered to be significant when $P < 0.05$. ED_{50} values for the methamphetamine dose–response curve and $T_{1/2}$ values for the time-course of methamphetamine discrimination after different pretreatments were defined as the dose or time connected with 50% methamphetamine-appropriate lever selection and were calculated using linear regression. Changes were considered to be significant when 95% confidence intervals of ED_{50} values or $T_{1/2}$ values did not overlap. In that case differences between two curves were further evaluated by using two-way ANOVA for repeated measures. SigmaStat program (Jandel Scientific, USA) was used.

3. Results

3.1. Establishment of discrimination baseline

Rats started to discriminate methamphetamine from saline reliably after approximately 30 days of training, but reaching the final level of accuracy (eight consecutive sessions with at least 90% of responses on the correct lever and no more than four incorrect responses during the first trial) required 40 to 80 sessions. Once the training criterion was reached, performance during training sessions was almost always maintained at 100% responding in all the subjects.

3.2. Substitution and pretreatment tests

Thioperamide did not generalize to the methamphetamine stimulus when given alone and did not attenuate the drug-appropriate responding when given together with the 1.0 mg/kg training dose of methamphetamine (Fig. 2). Thioperamide alone, at doses as high as 5.6 mg/kg, did not decrease the rate of responding, but when given together with the training dose of methamphetamine there was a marked and significant suppression of response rates [$F(4,36) = 11.242$, $P < 0.001$]. Responding completely stopped after 1.8 mg/kg of thioperamide in 1 of 10 subjects and after 3.0 mg/kg in 2 of 10 subjects when thioperamide was given with methamphetamine.

R-α-methylhistamine also did not substitute for methamphetamine when given alone and did not attenuate

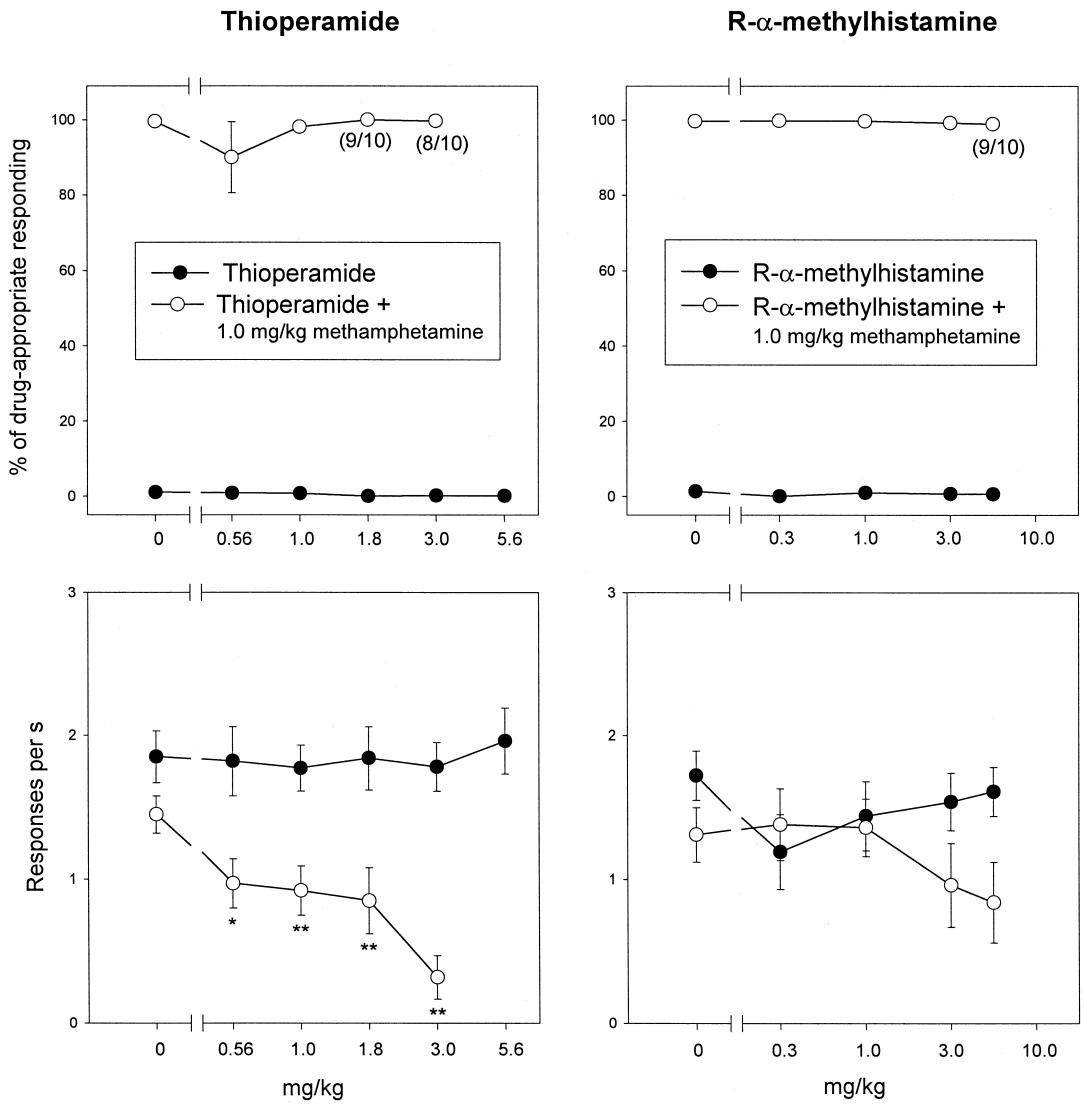

Fig. 2. Effects of thioperamide and *R*-α-methylhistamine in rats trained to discriminate 1.0 mg/kg of methamphetamine from saline. Data are means (±S.E.M.) from $n = 10$ rats. The percentage of methamphetamine-appropriate responding is shown as a function of dose during substitution test sessions (●) and during combination test sessions when the compounds were given together with the 1.0 mg/kg training dose of methamphetamine (○). Response rates are expressed as responses per second. $* P < 0.05$, $** P < 0.01$, post hoc comparison with the vehicle pretreatment after significant ANOVA for repeated measures main effect, Dunnett's test. Numbers in parentheses indicate the number of responding rats of the total number of rats in which the dose was tested.

the drug-appropriate responding when given together with the 1.0 mg/kg training dose of methamphetamine (Fig. 2). *R*-α-methylhistamine did not decrease response rates when given alone, but when the high 5.6 mg/kg dose of *R*-α-methylhistamine was given with 1.0 mg/kg of methamphetamine rate of responding decreased in approximately half of the rats and there was no responding in one of ten rats. However, the decrease in mean response rates was not significant.

3.3. Effects of pretreatments on the methamphetamine dose–response curve

A dose of 1.0 mg/kg of thioperamide shifted the methamphetamine dose–response curve to the left (Fig. 3), and this shift was statistically significant (non-overlapping 95% confidence intervals of thioperamide and saline pretreatments, Table 1). A significant difference between the methamphetamine dose–response curves after saline and thioperamide pretreatments was also revealed by two-way ANOVA: $F(1,18) = 17.694$, $P = 0.002$. Note that adding thioperamide to 0.3 mg/kg of methamphetamine produced almost 100% methamphetamine-appropriate responding even though this dose of methamphetamine when given alone produced only about 25% methamphetamine-appropriate responding.

In contrast to results with thioperamide, a dose of 3.0 mg/kg of *R*-α-methylhistamine did not produce any significant effect on the methamphetamine dose–response

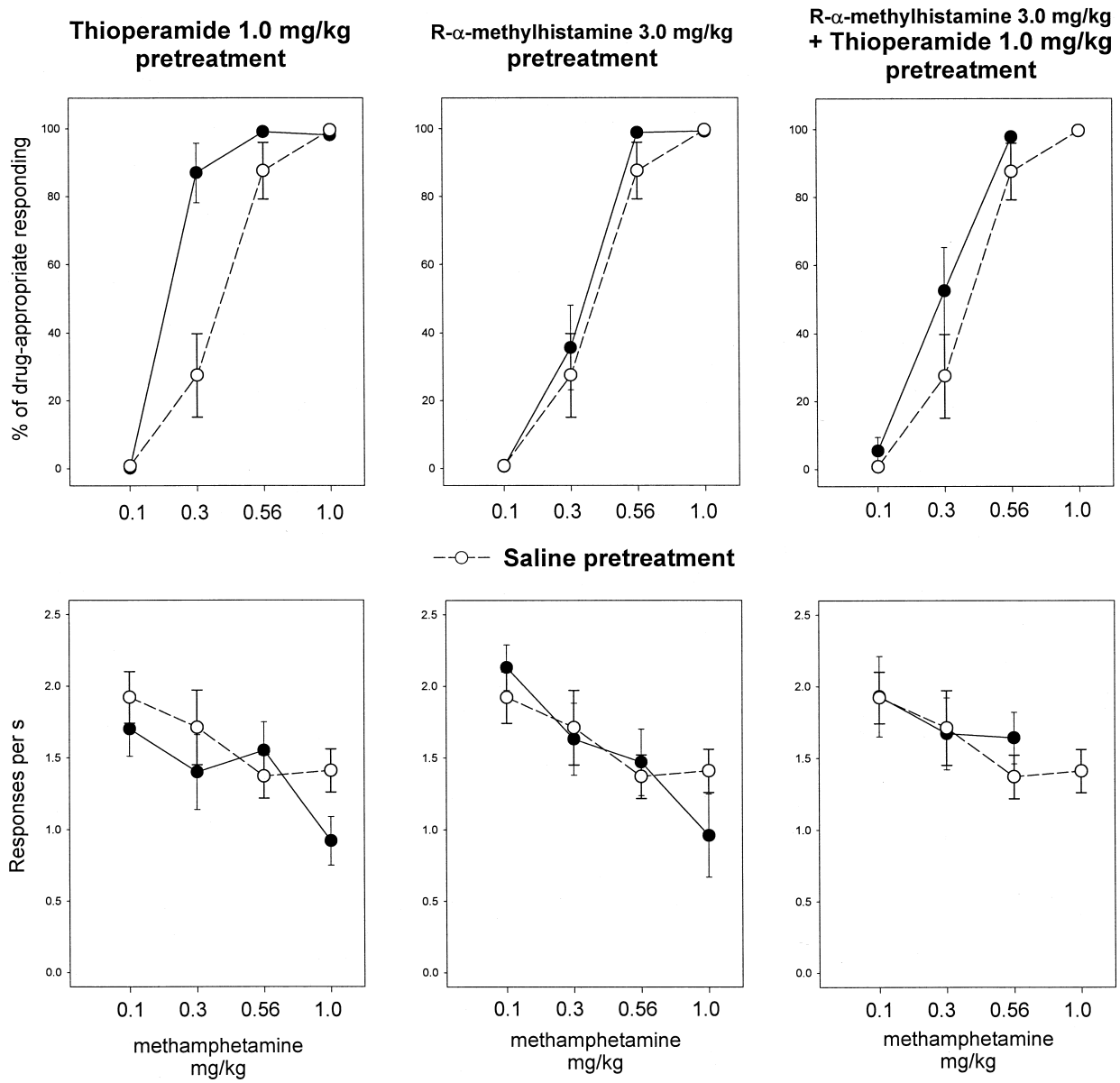

Fig. 3. Methamphetamine dose–response curves after pretreatment with 1.0 ml/kg of saline (○), 1.0 mg/kg of thioperamide, or 3.0 mg/kg of *R*-α-methylhistamine and after pretreatment with a combination of 1.0 mg/kg of thioperamide and 3.0 mg/kg of *R*-α-methylhistamine. Data are means (±S.E.M.) from $n = 10$ rats. The percentage of methamphetamine-appropriate responding is shown as a function of the dose of methamphetamine. Response rates are expressed as responses per second. ED_{50} values with 95% confidence intervals for the dose–response curves are presented in Table 1.

curve (overlapping 95% confidence intervals of *R*-α-methylhistamine and saline pretreatments, Fig. 3 and Table 1). However, this dose of *R*-α-methylhistamine (3.0 mg/kg) almost completely blocked the shift to the left of the methamphetamine dose–response curve produced by 1.0 mg/kg of thioperamide (Fig. 3). The dose–response

Table 1
ED_{50} values (95% confidence intervals) in mg/kg of methamphetamine for percentage of methamphetamine-appropriate responding when methamphetamine was administered with saline and with selected doses of thioperamide and *R*-α-methylhistamine

methamphetamine	+ saline (1.0 ml/kg)	0.46 (0.35–0.56)
methamphetamine	+ thioperamide (1.0 mg/kg)	0.26 (0.20–0.33)[a]
methamphetamine	+ *R*-α-methylhistamine (3.0 mg/kg)	0.34 (0.27–0.41)
methamphetamine	+ thioperamide (1.0 mg/kg) and *R*-α-methylhistamine (3.0 mg/kg)	0.31 (0.24–0.38)

[a] Non-overlapping 95% confidence intervals compared to the methamphetamine dose–response curve after saline pretreatment.

curve was still shifted somewhat to the left with about 50% generalization after the combination of thioperamide and *R*-α-methylhistamine with 0.3 mg/kg of methamphetamine, but the curve was no longer significantly different from that with saline pretreatment (overlapping 95% confidence intervals, Table 1).

3.4. Effects of pretreatments on the time-course of methamphetamine's discriminative-stimulus effects

A dose of 1.0 mg/kg of thioperamide markedly and significantly extended the time-course of discriminative-stimulus effects of both the 1.0 mg/kg training dose and a lower 0.3 mg/kg dose of methamphetamine (Fig. 4; non-overlapping 95% confidence intervals of thioperamide and saline pretreatments, Table 2). A significant difference between the time-course curves after saline and thioperamide pretreatments was also revealed by two-way ANOVA when both 1.0 mg/kg [$F(1,14) = 72.367$, $P < 0.001$] and 0.3 mg/kg [$F(1,12) = 48.205$, $P < 0.001$] doses of methamphetamine were used.

In contrast to thioperamide, a dose of 3.0 mg/kg of *R*-α-methylhistamine did not produce any significant change in the time-course curve for discriminative-stimulus effects of the 1.0 mg/kg training dose of methamphetamine (Fig. 4; overlapping 95% confidence intervals, Table 2). Adding 3.0 mg/kg of *R*-α-methylhistamine to the 1.0 mg/kg dose of thioperamide did not significantly reverse thioperamide's effects in extending the time-course

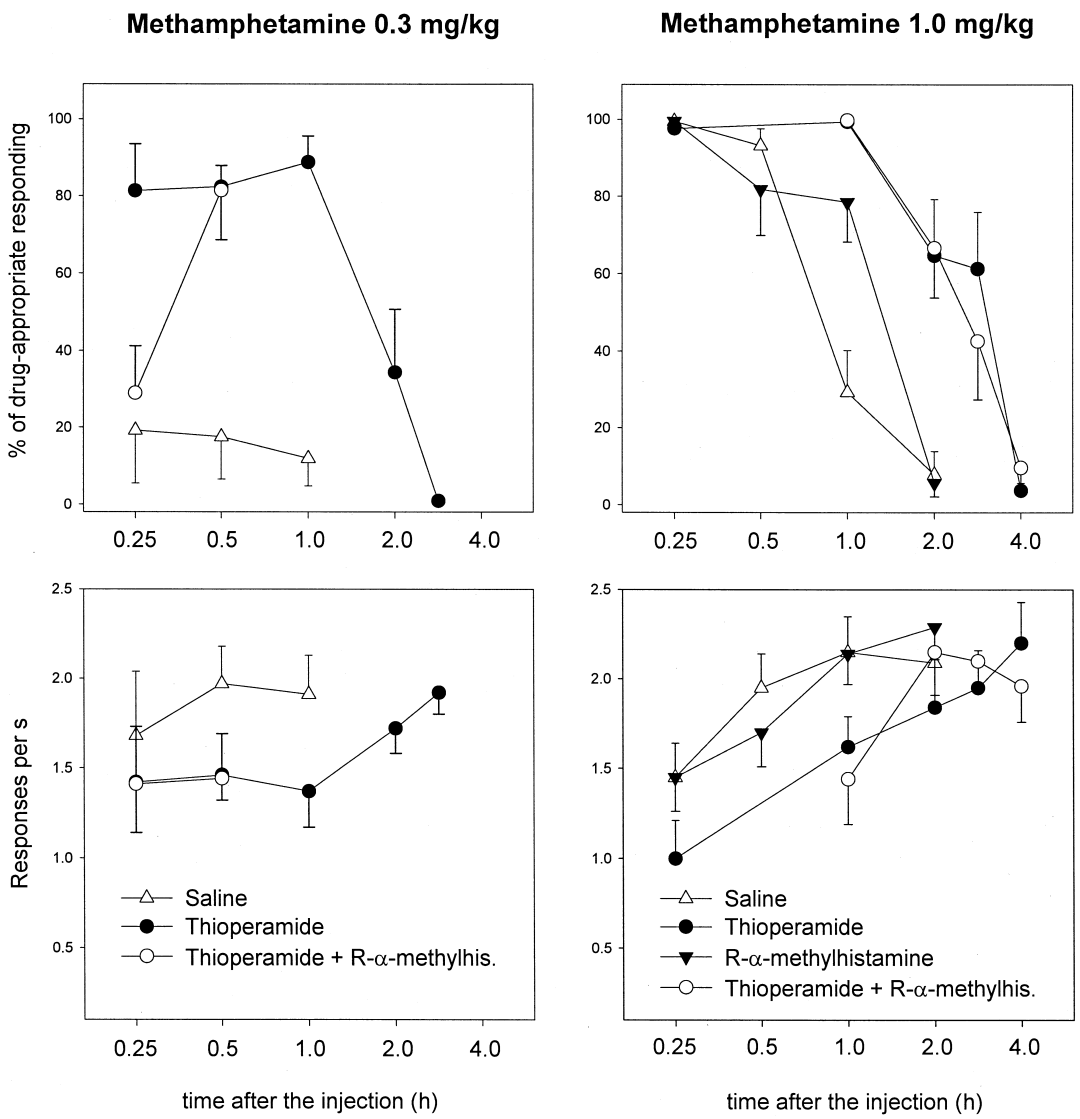

Fig. 4. Time-course curves for 1.0 mg/kg of methamphetamine (right panels) and for 0.3 mg/kg of methamphetamine (left panels) after pretreatment with 1.0 ml/kg of saline (open triangles), 1.0 mg/kg of thioperamide (filled circles), or 3.0 mg/kg of *R*-α-methylhistamine (filled triangles) and after pretreatment with a combination of 1.0 mg/kg of thioperamide and 3.0 mg/kg of *R*-α-methylhistamine (open circles). Data are means (±S.E.M.) from either $n = 8$ (1.0 mg/kg of methamphetamine) or $n = 7$ (0.3 mg/kg of methamphetamine) rats. The percentage of methamphetamine-appropriate responding is shown as a function of time after the injection of methamphetamine. Response rates are expressed as responses per second. $T_{1/2}$ values with 95% confidence intervals are presented in Table 2.

Table 2
$T_{1/2}$ values (95% confidence intervals) in hours for the methamphetamine time-course when 0.3 mg/kg and 1.0 mg/kg of methamphetamine were administered with saline and with selected doses of thioperamide and *R*-α-methylhistamine

Methamphetamine	0.3 mg/kg	1.0 mg/kg
+ saline (1.0 ml/kg)	> 0	1.07 (0.84–1.31)
+ thioperamide (1.0 mg/kg)	1.52 (1.09–1.95)[a]	2.75 (1.85–3.65)[a]
+ *R*-α-methylhistamine (3.0 mg/kg)	–	1.27 (0.84–1.68)
+ thioperamide (1.0 mg/kg) and *R*-α-methylhistamine (3.0 mg/kg)	–	2.66 (1.82–3.49)[a]

[a] Non-overlapping 95% confidence intervals compared to the methamphetamine time-course curve after saline pretreatment.

of 1.0 mg/kg dose of methamphetamine; the time-course curve remained significantly shifted to the right (Fig. 4; non-overlapping 95% confidence intervals of saline and the combination of thioperamide and *R*-α-methylhistamine, Table 2). However, 3.0 mg/kg of *R*-α-methylhistamine did reverse the effects of 1.0 mg/kg of thioperamide on the discriminative-stimulus effects of the lower 0.3 mg/kg dose of methamphetamine, but this blocking effect disappeared when a longer pretreatment time was used (Fig. 4; since the methamphetamine-appropriate responding increased rather than decreased through the time-course experiment, $T_{1/2}$ values could not be determined).

4. Discussion

The aim of the present experiment was to assess the role of histamine H_3 receptors in methamphetamine's discriminative-stimulus effects in rats. The histamine H_3 receptor antagonist thioperamide, which promotes histamine release, shifted the dose–response curve for the discriminative-stimulus effects of methamphetamine significantly to the left and markedly extended the time-course of the methamphetamine discrimination. In contrast, the histamine H_3 receptor agonist *R*-α-methylhistamine, which blocks histamine release, produced no effects when given alone, but attenuated the effects of thioperamide on the methamphetamine dose–response curve when both drugs were given together. Neither thioperamide alone nor *R*-α-methylhistamine alone substituted for the training dose of methamphetamine and both compounds were not able to alter the discriminative-stimulus effects of methamphetamine when given together with the training dose of 1.0 mg/kg methamphetamine. However, when thioperamide was given together with the 1.0 mg/kg training dose of methamphetamine, it significantly suppressed the rate of responding.

The marked effect of thioperamide pretreatment in the present experiment suggests that elevated brain histamine plays an important role in methamphetamine's discriminative-stimulus actions. This is in line with neurochemical findings of increased brain histamine levels after administration of methamphetamine (Ito et al., 1996a,b). In contrast to other monoaminergic systems where brain levels reach their peak within 10 to 30 min after methamphetamine administration (Kuczenski et al., 1995; Melega et al., 1995), brain histamine levels have been reported to be maximal 40 to 160 min after methamphetamine administration (Ito et al., 1997b), which might explain why the effects of thioperamide pretreatment in the present experiment were so marked in the time-course study. The lack of generalization of thioperamide to the methamphetamine discriminative-stimulus when it was given alone is in agreement with the fact that thioperamide has potent effects on brain histamine turnover only when histamine release is stimulated by other drugs and does not influence steady-state brain histamine levels (Oishi et al., 1989).

Blockade of histamine H_3 heteroreceptors located presynaptically in other neurotransmitter systems might contribute to the thioperamide's effects in the present experiment, since histamine H_3 receptors are not restricted to histaminergic neurons (Schwartz et al., 1991). High densities of histamine H_3 receptors are found especially in dopaminergic brain areas such as the nucleus accumbens, striatum and substantia nigra (Pollard et al., 1993). The dopaminergic system appears to play a dominant role in the discriminative-stimulus effects of methamphetamine (Sasaki et al., 1995; Munzar et al., 1998a; Tidey and Bergman, 1998) and could be involved in the present effects with thioperamide, since histamine may inhibit dopamine release in the striatum via histamine H_3 heteroreceptors (Schlicker et al., 1993). Possible involvement of noradrenergic and serotonergic neurotransmitter systems also can not be excluded (Fink et al., 1990; Timm et al., 1998).

Thioperamide is a relatively selective histamine H_3 receptor antagonist, but it has some affinity for other receptor systems, especially for 5-HT_3 receptors, and can act at these receptors as an antagonist (Leurs et al., 1995). Potentiation of the discriminative-stimulus effects of both amphetamine (West et al., 1995) and methamphetamine (Munzar et al., 1998b) in rats by 5-HT_3 receptor antagonists has been observed and, thus, thioperamide's 5-HT_3 receptor antagonist properties could contribute to it's potentiation of the discriminative-stimulus effects of methamphetamine in the present experiment.

Although most of thioperamide's effects are mediated by interaction with histamine H_3 receptors, higher doses of

thioperamide have been reported to inhibit monoamine oxidase of both B and A subtypes in the rat brain in vitro by non-specific mechanisms (Sakurai et al., 1995). This effect of thioperamide might contribute to the observed interaction with methamphetamine, since amphetamine's discriminative-stimulus properties are enhanced by drugs that block monoamine oxidase activity (Yasar et al., 1993). Non-receptor mediated actions of thioperamide might, furthermore, affect either redistribution of methamphetamine from the brain or methamphetamine metabolism and this might contribute to the robust effects of thioperamide in the time-course study. However, this could not play a major role in the present experiment, since thioperamide also markedly potentiated effects of a low 0.3 mg/kg dose of methamphetamine that by itself produced only threshold effects when given 15 min before the session, i.e., at the time when brain levels and both behavioral and neurochemical effects of methamphetamine appear to be maximal (Kuczenski et al., 1995; Melega et al., 1995).

Although the shift to the left of the methamphetamine dose–response curve produced by thioperamide in the present experiment was almost completely blocked by co-administration of *R*-α-methylhistamine, *R*-α-methylhistamine did not attenuate thioperamide's effects on the time-course of discriminative-stimulus effects of the 1.0 mg/kg training dose of methamphetamine. Since *R*-α-methylhistamine can fully block most behavioral effects of thioperamide (Clapham and Kilpatrick, 1994; Lambert et al., 1998), the lack of effects in the present time-course experiment was unexpected and may be related to pharmacokinetic factors. Thioperamide's half-life is between 2 to 10 h, depending on dose (Silva et al., 1997), whereas *R*-α-methylhistamine is eliminated much faster in rats (Yamasaki et al., 1994). Although both thioperamide and *R*-α-methylhistamine cross the blood–brain barrier (Oishi et al., 1989; Mochizuki et al., 1996), thioperamide is a rather lipophilic substance (see Fig. 1) that remains in the brain and binds strongly to lipophilic tissues (Silva et al., 1997), whereas *R*-α-methylhistamine is redistributed to other body compartments (Yamasaki et al., 1994).

Rate-suppressing effects of thioperamide given together with the training dose of methamphetamine support previous findings that thioperamide attenuates amphetamine-induced locomotor activity (Clapham and Kilpatrick, 1994). However, the marked suppression of responding in the present experiment likely reflects an interaction between thioperamide and methamphetamine rather than simple blocking of stimulant-induced activity.

If histamine release contributes to methamphetamine's discriminative-stimulus actions, as suggested by the present findings, antagonists at post-synaptic histamine H_1 and H_2 receptors would be expected to block methamphetamine's discriminative-stimulus effects. In contrast, in most studies, antagonists at post-synaptic histamine receptors generalized, at least partially, to the discriminative-stimulus effects of amphetamines (Evans and Johanson, 1989; Yasar et al., 1992; Suzuki et al., 1996, 1997) and potentiated the rewarding effects of methamphetamine (Masukawa et al., 1993). However, these effects of antihistamines may be related to their relative lack of selectivity and are probably mediated more by their inhibition of dopamine uptake than by their actions at histamine receptors, as suggested by Masukawa et al. (1993) and Suzuki et al. (1997).

In conclusion, it has been demonstrated that the histamine H_3 receptor antagonist thioperamide potentiates methamphetamine's discriminative-stimulus effects in rats. Facilitation of methamphetamine-induced elevation of brain histamine levels by blockade of histamine H_3 autoreceptors may explain this finding as well as elevation of other brain neurotransmitters by blockade of histamine H_3 heteroreceptors. A possible role of thioperamide's action at 5-HT_3 receptors as well as non-receptor mediated inhibition of brain monoamine oxidase induced by thioperamide or a pharmacokinetic interaction between thioperamide and methamphetamine also cannot be excluded. Potentiation of methamphetamine's discriminative-stimulus effects by thioperamide is, however, partially reversed by the histamine H_3 receptor agonist *R*-α-methylhistamine, suggesting a major role of histamine H_3 receptors in these actions of thioperamide.

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