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ORIGINAL INVESTIGATION

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Role of 5-HT_{2A} and 5-HT_{2C} receptors in the stimulus effects of hallucinogenic drugs II: reassessment of LSD false positives

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Abstract In the context of animal studies of hallucinogens, an LSD-false positive is defined as a drug known to be devoid of hallucinogenic activity in humans but which nonetheless fully mimics LSD in animals. Quipazine, MK-212, lisuride, and yohimbine have all been reported to be LSD false positives. The present study was designed to determine whether these compounds also substitute for the stimulus effects of the more pharmacologically selective hallucinogen (−)DOM (0.56 mg/kg, 75-min pretreatment time). The LSD and (−)DOM stimuli fully generalized to quipazine (3.0 mg/kg) and lisuride (0.2 mg/kg), but only partially generalized to MK-212 (0.1–1.0 mg/kg) and yohimbine (2–20 mg/kg). In combination tests, pirenpirone (0.08 mg/kg), a compound with both D_2 and 5-HT_{2A} affinity, blocked the substitution of quipazine and lisuride for the (−)DOM stimulus. Ketanserin (2.5 mg/kg), an antagonist with greater than 1 order of magnitude higher affinity for 5-HT_{2A} receptors than either 5-HT_{2C} or D_2 receptors, also fully blocked the substitution of these compounds for the (−)DOM stimulus, while the selective D_2 antagonist thiothixene (0.1–1.0 mg/kg) failed to block the substitution of lisuride for the (−)DOM stimulus. These results suggest that quipazine and lisuride substitute for the stimulus properties of the phenylalkglamine hallucinogen (−)DOM via agonist activity at 5-HT_{2A} receptors. In addition, these results suggest that 5-HT_{2A} agonist activity may be required, but is not in itself sufficient, for indolamine and phenylalkglamine compounds to elicit hallucinations in humans. Finally, it is concluded that MK-212 and yohimbine are neither LSD nor (−)DOM false positives.

Key words Drug-induced stimulus control · Hallucinogens · 5-HT_{2A} · 5-HT_{2C} · LSD (lysergic acid diethylamide) · DOM (2,5-dimethoxy-4-methylamphetamine)

Introduction

Over the past 2 decades, drug-induced stimulus control has been applied to the study of hallucinogenic drugs (Winter 1978a, 1994; Appel et al. 1982; Glennon et al. 1984). The stimulus effects of LSD (Hirschorn and Winter 1971) and DOM (Silverman and Ho 1978) have been extensively studied in animal subjects, with the ultimate goal of elucidating the mechanisms which underlie the unique ability of these agents to elicit hallucinations in humans (for reviews see Glennon 1982; Appel and Cunningham 1986).

However, while humans can verbally describe the subjective effects created by a given psychoactive substance and thereby verify that a substance does, in fact, induce hallucinations, the true qualitative nature of the interoceptive state governing hallucinogen-induced stimulus control in a non-verbal animal species is not accessible. Thus, although hallucinogenic agents can serve as effective discriminative stimuli in animal subjects, the investigator cannot absolutely determine whether the interactions which mediate stimulus control in the trained animal subject are identical to or even related to the interactions which are responsible for the induction of hallucinations in humans.

This potential shortcoming of the drug-induced stimulus control paradigm is underscored by the existence of compounds which do not elicit hallucinations in humans, but have been reported to cross-generalize

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with the LSD stimulus, i.e., LSD-false positives (for review see Winter 1994). Four such compounds have been identified: quipazine (Colpaert et al. 1979; Winter 1979; Parati et al. 1980), MK-212 (White and Appel 1982c; Cunningham et al. 1986; Lowy and Meltzer 1988), lisuride (Freedman and Boggan 1982; White and Appel 1982a,b) and yohimbine (Holmberg et al. 1961; Colpaert 1984).

There are two possible explanations for these observations. LSD has been described to bind serotonergic, adrenergic and dopaminergic receptors with high affinity (Burt et al. 1976; Creese et al. 1976; U'Prichard et al. 1977; Meibach et al. 1980; Leysen 1985; Hoyer 1988; Leysen et al. 1989). This complex pharmacological profile may result in a compound discriminative stimulus (Ator and Griffiths 1989) which is mediated by interactions with receptors which are both essential for and extraneous to LSD hallucinogenesis. Therefore, it is conceivable that the substitution of a non-hallucinogenic compound for the LSD stimulus could be mediated exclusively by receptors which mediate the stimulus effects of LSD but which are peripheral to the mechanism by which LSD elicits hallucinations in humans. Thus, the interactions responsible for the substitution of non-hallucinogenic compounds for the LSD stimulus may be considered epiphenomena (White 1986) unrelated to the central effect of LSD-induced hallucinogenesis. Alternatively, these non-hallucinogenic compounds may substitute for the LSD stimulus by interacting with receptors which mediate the stimulus effects of LSD, but represent only a subset of those interactions required for hallucinogenesis in humans. While these compounds might fully substitute for the LSD stimulus, they would lack some of the elements required for the induction of hallucinations in humans, and therefore would fail to induce hallucinations when administered alone.

Because of the complexity of the LSD stimulus, it is difficult to determine which of these two mechanisms accounts for the observations of false positives in the model of LSD-induced stimulus control. For this reason, DOM was employed as a training stimulus in the present study. Biochemical studies have demonstrated that the pharmacological profile of the phenylalkglamine hallucinogen DOM is far less complex than that of LSD (Leysen et al. 1989). DOM has been reported to bind selectively to serotonin (5-hydroxytryptamine, 5-HT) 5-HT_2 receptor subtypes. Correspondingly, the stimulus effects of DOM may be less complex than those of LSD (for review see Glennon 1990).

Additional selectivity for the study of the hallucinogenic effects of indolamine/phenylalkglamine compounds might be achieved by employing the (−)isomer of DOM in discrimination studies. In clinical studies, the (+)isomer of DOM elicited primarily non-hallucinogenic subjective effects, while the (−)isomer more selectively elicited LSD-like hallucinogenic effects in humans (Shulgin et al. 1973; Shulgin and Shulgin 1991). The (−)DOM stimulus fully substitutes for the LSD stimulus in a time-dependent manner, eliciting maximal LSD-like effects at the 75-min pretreatment time. Stable stimulus control can be achieved with (−)DOM (0.56 mg/kg) when the 75-min pretreatment time is employed (Fiorella et al. 1995b).

The present study was designed to investigate the stimulus effects of quipazine, MK-212, lisuride, and yohimbine in both LSD and (−)DOM-trained subjects. The interactions of these compounds in the more selective paradigm of (−)DOM-induced stimulus control will potentially offer insight into the nature of the hallucinogenic stimulus.

Materials and methods

Animals

Male Fischer 344 rats were obtained from Harlan Sprague-Dawley Inc. (Indianapolis, Ind.). They were housed in pairs under a 12-h alternating light-dark cycle and allowed free access to water in the home cage. Subjects were fed immediately following experimental sessions. Caloric intake was controlled to yield a mean body weight of 250 g.

Apparatus

Two small animal test chambers (Coulbourn Instruments Model E10-10) housed in larger light-proof, sound insulated boxes were used for all experiments. Each box had a house light and exhaust fan. The chamber contained two levers mounted on opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml sweetened condensed milk diluted 2:1 with tap water.

Drug-induced stimulus control procedure

Forty-five subjects were trained to discriminate LSD (0.1 mg/kg, 15-min pretreatment, intraperitoneal injection) from saline, and 15 subjects were trained to discriminate (−)DOM (0.56 mg/kg, 75-min pretreatment time, intraperitoneal injection) from saline as described previously (Fiorella et al. 1995b). A fixed ratio 10 (FR10) schedule of reinforcement was used. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to the delivery of the first reinforcer were on the appropriate lever.

After stimulus control with the training drug was well established, tests of generalization (substitution tests) and tests of antagonism (combination tests) were conducted once per week in each animal so long as performance did not fall below a criterion level of 83% correct responding in any one of the previous three training sessions conducted during that week.

Test procedure

During test sessions, no responses were reinforced and the session was terminated after the emission of ten responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection,

that is, prior to the emission of ten responses on either lever, by the elapsed time. The data for subjects failing to emit ten responses within the constraints of the 10-min test session were considered in the calculation of response rate but not in the calculation of percent drug-appropriate responding. Pretreatment times were 15 min for lisuride and yohimbine, and 25 min for quipazine and MK-212. Antagonists were administered at a pretreatment time of 75 min. Pretreatment times and doses are based on the results of reports in the literature and preliminary experiments (Fiorella et al. 1995a).

Drugs

LSD and (−)DOM were obtained from the National Institute on Drug Abuse. Quipazine, yohimbine, and lisuride were purchased from Research Biochemicals International (Natick, Mass.). MK-212 was a generous gift from Merck Research Laboratories (West Point, Pa.). Ketanserin, pirenpirone, quipazine, MK-212, and lisuride were dissolved in a small volume of ethanol, yohimbine was dissolved in a small volume of 8.5% lactic acid, LSD, (−)DOM and thiothixene were dissolved in water, and then further diluted with water to make a concentrated stock solution. Stock solutions were diluted to the appropriate concentrations with 0.9% saline. All solutions were injected in a volume of 1.0 ml/kg body weight.

Data analysis

The criteria for substitution and antagonism were based on the results of individual applications of the paired Wilcoxon's signed ranks test: 1) full substitution/no antagonism: the test compound or combination elicits a level of drug-appropriate responding not significantly different from that elicited by the drug training condition; 2) partial substitution/partial antagonism: the test compound or combination elicits a level of drug-appropriate responding significantly different from both the drug and saline training conditions; 3) no substitution/full antagonism: the test compound or combination elicits a level of drug-appropriate responding not significantly different from the saline training condition.

Results

Subjects acquired LSD and (−)DOM-induced stimulus control after an average of 28.9 (SEM ± 1.6) and 37.5 (0.93) training sessions, respectively. Drug-appropriate responding followed an orderly dose-response relationship in both groups of subjects (Fig. 1). The training doses of LSD (0.1 mg/kg) and (−)DOM (0.56 mg/kg) elicited 98.2% and 99.3% drug-appropriate responding, respectively.

In tests of generalization, quipazine (3.0 mg/kg) and lisuride (0.2 mg/kg) fully substituted for the (−)DOM stimulus, eliciting 97.4% (1.7) and 96.8% (1.7) (−)DOM-appropriate responding, respectively (Fig. 2). In contrast, MK-212 (0.1–0.66 mg/kg) and yohimbine (2–20 mg/kg) only partially substituted for the (−)DOM stimulus, eliciting 81.6% (10.0) and 39.2% (14.1) (−)DOM-appropriate responding, respectively. Maximal MK-212-elicited (−)DOM-appropriate responding was observed after the administration of 0.5 mg/kg. Increasing the dose to 0.66 mg/kg resulted in a diminution of (−)DOM-appropriate responding, and further increases in dose were not compatible with test session completion. Maximal yohimbine-elicited (−)DOM-appropriate responding was observed after administration of 9 mg/kg. Further increases in the test dose of yohimbine (20 mg/kg) resulted in complete suppression of responding (none of six tested subjects completed the test session).

In the LSD-trained subjects, quipazine (3.0 mg/kg) and lisuride (0.2 mg/kg) fully substituted for the training stimulus, eliciting 89.0% (4.1) and 93.3% (3.9) LSD-appropriate responding, respectively. MK-212

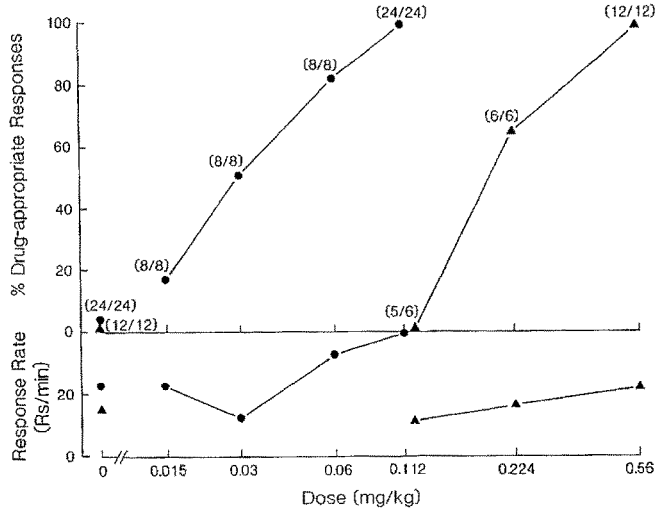

Fig. 1 The dose-effect relationships for the training drugs in the LSD- (*circles*) and (−)DOM- (*triangles*) trained subjects. *Ordinate*: *above* – percentage of responses emitted on the drug-appropriate lever, *below* – responses per minute. *Abscissa*: dose of training drug. The number of subjects completing the test session, and the number of subjects participating in each test session, is expressed as a ratio adjacent to each of the points

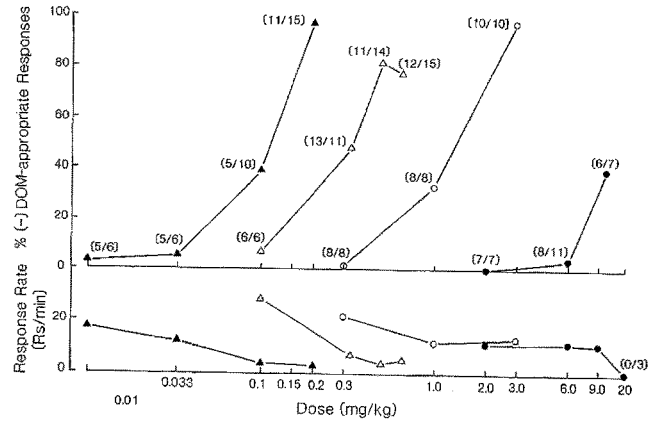

Fig. 2 The stimulus effects of lisuride (15-min pretreatment time; *closed triangles*), MK-212 (25-min pretreatment time; *open triangles*), quipazine (25-min pretreatment time; *open circles*), and yohimbine (15-min pretreatment time; *closed circles*) in (−)DOM-trained subjects (0.56 mg/kg, 75-min pretreatment time). The number of subjects completing the test session, and the number of subjects participating in each test session, is expressed as a ratio adjacent to each of the points. *Ordinate*: *above* – percentage of responses emitted on the (−)DOM-appropriate lever, *below*: responses per minute. *Abscissa*: dose (mg/kg) of test compound

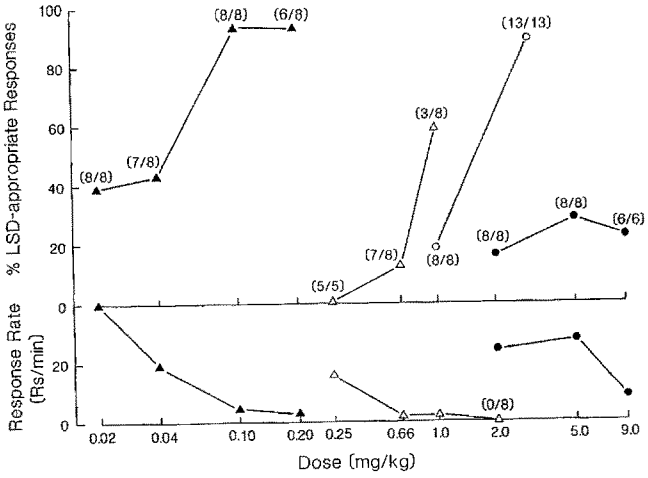

Fig. 3 The stimulus effects of lisuride (15-min pretreatment time; *closed triangles*), MK-212 (25-min pretreatment time; *open triangles*), quipazine (25-min pretreatment time; *open circles*), and yohimbine (15-min pretreatment time; *closed circles*) in LSD-trained subjects (0.1 mg/kg, 15-min pretreatment time). The number of subjects completing the test session, and the number of subjects participating in each test session, is expressed as a ratio adjacent to each of the points. *Ordinate*: *above* – percentage of responses emitted on the LSD-appropriate lever, *below* – responses per minute. *Abscissa*: dose (mg/kg) of test compound

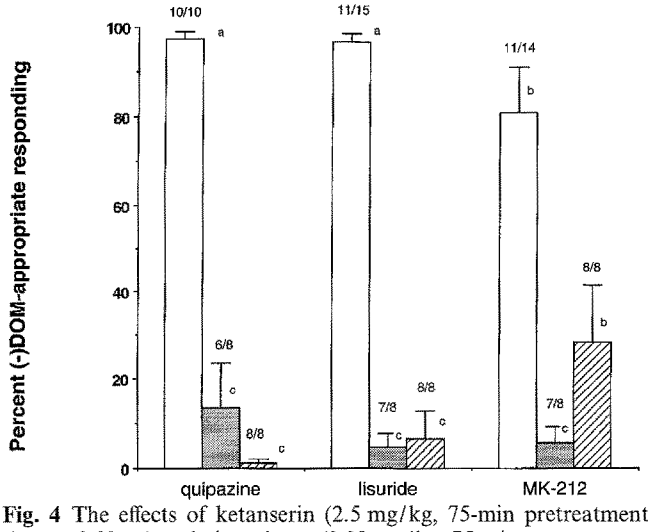

Fig. 4 The effects of ketanserin (2.5 mg/kg, 75-min pretreatment time; *solid bars*) and pirenpirone (0.08 mg/kg, 75-min pretreatment time; *hatched bars*) on the substitution of quipazine (3.0 mg/kg, 25-min pretreatment time), lisuride (0.2 mg/kg, 15-min pretreatment time), and MK-212 (0.5 mg/kg, 25-min pretreatment time) for the (−)DOM stimulus. *Open bars* represent the percentage of responses emitted on the (−)DOM-appropriate lever following the administration of the test compounds alone. The number of subjects completing the test session, and the number of subjects participating in each test session, is expressed as a ratio adjacent to each of the bars. *Ordinate*: percentage of responses emitted on the (−)DOM-appropriate lever. [a]Percent (−)DOM-appropriate responding not different from the (−)DOM-training condition, [b]percent (−)DOM-appropriate responding significantly different from both the (−)DOM and saline training condition ($P < 0.05$), [c]percent (−)DOM-appropriate responding not significantly different from the saline training condition

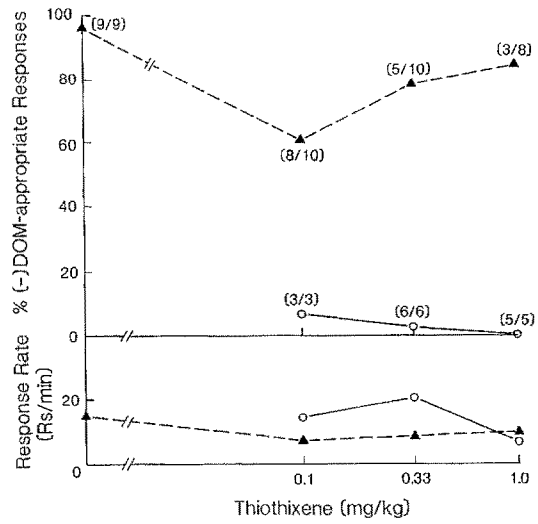

Fig. 5 Dose-inhibition plot for thiothixene. Thiothixene (75-min pretreatment time) was administered alone (*open circles*) or in combination with 0.2 mg/kg lisuride (20-min pretreatment time, *closed triangles*). The number of subjects completing the test session, and the number of subjects participating in each test session, is expressed as a ratio adjacent to each of the points. *Ordinate*: *above* – percentage of responses emitted on the (−)DOM-appropriate lever, *below*– responses per minute. *Abscissa*: dose (mg/kg) of thiothixene

(0.1–2.0 mg/kg) elicited 58.7% (21.7) (−)DOM-appropriate responding. However, at the dose of MK-212 required to elicit this response (1.0 mg/kg), only three of eight subjects completed the test session. As a result, no statistical statement can be made with respect to the level of substitution observed at this dose. Yohimbine only partially substituted for the LSD stimulus, eliciting a maximum of 28.6% (14.1) (−)DOM-appropriate responding at doses which were compatible with test session completion (Fig. 3).

In combination tests, both 2.5 mg/kg ketanserin and 0.08 mg/kg pirenpirone, fully antagonized the substitution of 3.0 mg/kg quipazine and 0.2 mg/kg lisuride for the (−)DOM stimulus (Fig. 4). In contrast, pirenpirone failed to antagonize completely the partial substitution of MK-212 for the (−)DOM stimulus.

Thiothixene (0.1–1.0 mg/kg) failed to antagonize the substitution of 0.2 mg/kg lisuride for the (−)DOM stimulus at the doses tested (Fig. 5). One of the subjects died within 24 h of the test session in which the highest dose of thiothixene was administered (1.0 mg/kg) in combination with lisuride (0.2 mg/kg). In addition, the same doses of thiothixene failed to antagonize the (−)DOM stimulus (data not shown).

Discussion

The present study was designed to investigate the stimulus effects of four purported LSD-false positive compounds (quipazine, MK-212, lisuride, and yohimbine) in experimental groups trained to discriminate either

(−)DOM (0.56 mg/kg) or LSD (0.1 mg/kg) from saline.

In tests of generalization, the quipazine and lisuride stimuli fully substituted for both the (−)DOM and LSD stimuli. Correspondingly, these compounds can appropriately be termed hallucinogen false positives. In contrast, MK-212 and yohimbine did not fully substitute for the stimulus effects of either (−)DOM or LSD (Figs 2 and 3).

The present observations are in agreement with the findings of a previous study (Winter 1978b) in which the yohimbine stimulus did not generalize to the LSD stimulus. However, they fail to replicate the findings of Colpaert (1984), who reported the cross-generalization of the LSD and yohimbine discriminative stimuli. In addition, the results are not in agreement with those of White and Appel (1982c), who reported the full substitution of MK-212 for the LSD stimulus (0.8 mg/kg).

On the basis of biochemical data, the investigation of the mechanism by which the false positive compounds, lisuride and quipazine, substitute for the (−)DOM and LSD stimuli was focused on the 5-HT_{2A} receptor. In radioligand binding studies, both quipazine and lisuride have been demonstrated to possess high affinity for the 5-HT_{2A} and 5-HT_{2C} receptors (Hoyer 1988). With respect to the stimulation of phosphoinositide (PI) turnover, quipazine and lisuride have been reported to act as partial agonists at 5-HT_{2A} receptors (Conn and Sanders-Bush 1987; Burris et al. 1991). While quipazine also exhibits agonist activity at 5-HT_{2C} receptors (Conn and Sanders-Bush 1987), lisuride has been reported to act as a pure antagonist at these receptors (Burris et al. 1991). Hallucinogens of the phenylalkglamine and indolamine type, including (−)DOM, have also been demonstrated to possess both high affinity and partial agonist activity at the 5-HT_{2A} site (Sanders-Bush et al. 1988). Thus, while each of the drugs considered in the present study interacts with a variety of receptors, their pharmacological profiles appear to converge only with respect to partial agonist activity at 5-HT_{2A} receptors.

When pirenpirone was administered in combination with quipazine and lisuride, the substitution of these agents for the (−)DOM stimulus was completely antagonized (Fig. 4). While pirenpirone possesses more than 30 times higher affinity for the 5-HT_{2A} receptor than the 5-HT_{2C} receptor (Fiorella et al. 1995a), it also has high affinity for the dopaminergic D_2 receptor (Kennis et al. 1986). For this reason, ketanserin was also administered in combination with the false positive agents. Ketanserin, like pirenpirone, has approximately 30 times higher affinity for 5-HT_{2A} then 5-HT_{2C} receptors (Fiorella et al. 1995a), but it does not exhibit the same high affinity for the D_2 receptor (Van Wijngaarden et al. 1990). Ketanserin also completely blocked the substitution of the false positive compounds for the (−)DOM stimuli. The results of these combination tests further support the hypothesis that the substitution of the false positive compounds for the (−)DOM stimulus is mediated by agonist activity at the 5-HT_{2A} receptor.

It is of interest to note that pirenpirone failed to antagonize completely the partial substitution of MK-212 for the (−)DOM stimulus. This result may indicate a role for non-5-HT_{2A} receptors in the partial substitution of MK-212 for the (−)DOM stimulus. While MK-212 is a partial agonist with respect to the stimulation of PI turnover at the 5-HT_{2A} receptor (Conn and Sanders-Bush 1987), radioligand binding studies have demonstrated that this compound possesses relatively low affinity for this site (Hoyer 1988). As a result, the magnitude of the interaction of MK-212 with 5-HT_{2A} sites in vivo may not be sufficient to elicit substitution for the hallucinogenic discriminative stimuli. Previous behavioral and biochemical studies have indicated that agonist interactions at 5-HT_{2C} receptors may play a predominant role in the pharmacological effects of MK-212 Cunningham et al. 1986; Conn and Sanders-Bush 1987; Hoyer 1988). Therefore, interactions with these receptors, in addition to 5-HT2A receptors, may mediate the partial substitution of MK-212 for the (−)DOM stimulus.

The indirect activation of 5-HT_{2A} receptors by these false positive compounds provides an additional consideration in the present study. This is of particular importance in the case of lisuride. The elegant work of White and associates (for review see White 1986) demonstrated that the stimulus effects of lisuride are primarily mediated by agonist interactions at dopaminergic receptors (White and Appel 1982a). In a series of lisuride-LSD discrimination experiments, apomorphine, a dopaminergic agonist, elicited lisuride-appropriate responding, while quipazine, a serotonergic compound, consistently elicited LSD-appropriate responding (White and Appel 1982b). In addition, a substantial amount of both behavioral and biochemical evidence indicates that serotonin receptors can be indirectly activated via agonist interactions at dopaminergic sites (Maj et al. 1974). So, while DOM has been reported to possess negligible affinity for dopaminergic receptors (Leysen et al. 1989), it is possible that a compound could substitute for DOM by interacting primarily with dopaminergic receptors to stimulate the release of serotonin and thereby indirectly activate serotonergic receptors. For this reason, thiothixene was administered in combination with lisuride to the (−)DOM trained subjects. Thiothixene was chosen on the basis of a previous study by Meltzer et al. (1989) who reported that, of a large series of dopaminergic antagonists, thiothixene possessed the highest level of selectivity for the D_2 receptor with respect to the 5-HT_{2A} receptor. Thiothixene did not, at any dose, significantly antagonize the substitution of lisuride for the (−)DOM stimulus (Fig. 5). These data suggest that

the ability of lisuride to substitute for the (−)DOM stimulus does not rely on agonist interactions with dopaminergic receptors, but direct agonist interactions with 5-HT_{2A} receptors.

Taken together, the present data indicate that quipazine and lisuride substitute not only for the stimulus effects of LSD, but also for the stimulus effects of the pharmacologically more selective hallucinogen (−)DOM. Therefore, these compounds can now be classified as hallucinogen false positives. For the following reasons, we hypothesize that the substitution of these non-hallucinogenic compounds for the stimulus effects of hallucinogens is due to a common agonist interaction with 5-HT_{2A} receptors: 1) LSD and (−)DOM, as well as the two false positive compounds, exhibit both high affinity (Hoyer 1988; Titeler et al. 1988) and partial agonist activity at 5-HT_{2A} receptors with respect to the stimulation of PI turnover (Conn and Sanders-Bush 1987; Burris et al. 1991); 2) antagonists of the 5-HT_{2A} receptor block the substitution of quipazine and lisuride for the (−)DOM stimulus.

Because there is no evidence that quipazine and lisuride are hallucinogenic in humans, we further hypothesize that while 5-HT_{2A} agonist activity plays a leading role in the stimulus effects of hallucinogenic compounds, this characteristic is not unique to compounds which elicit hallucinations in humans. The apparent ubiquity and prominence of 5-HT_{2A} affinity and agonist activity in the pharmacological profile of the phenethylamine and indolamine hallucinogens implies its requirement for hallucinogenesis in humans (Titeler et al. 1988; Glennon 1990; Fiorella et al. 1995c). However, the apparent prominence of 5-HT_{2A} agonist activity in the stimulus effects of the false positive compounds appears to indicate that it alone is not sufficient for the induction of hallucinations in humans. Thus, when considered in the context of previous studies, the present data suggest that 5-HT_{2A} agonist activity is not an epiphenomenon, unrelated to the hallucinogenic effects of phenethylamine/indolamine compounds, but that additional pharmacological activity is required to complete the spectrum of interactions required for hallucinogenesis.

Burris et al. (1991) have hypothesized that the simultaneous presence of agonist activity at 5-HT_{2C} and 5-HT_{2A} receptors may satisfy the criteria required for hallucinogenic activity. Several important findings support this contention: 1) hallucinogens bind with high affinity at both 5-HT_{2C} and 5-HT_{2A} receptors (Titeler et al. 1988); 2) while the non-hallucinogenic congeners of LSD act as partial agonists at 5-HT_{2A} receptors, only LSD acts as a partial agonist at both 5-HT_{2A} and 5-HT_{2C} receptors with respect to the stimulation of PI turnover (in vitro) (Burris et al. 1991); 3) the potency of hallucinogens to substitute for the DOM stimulus and to elicit hallucinations in humans correlates significantly with affinity for both 5-HT_{2A} and 5-HT_{2C} receptors (Titeler et al. 1988).

Despite the attractiveness of the hypothesis that the simultaneous presence of agonist activity at 5-HT_{2A} and 5-HT_{2C} receptors comprises the spectrum of interactions necessary for hallucinogenesis, several lines of evidence are difficult to reconcile. Agonist activity at 5-HT_{2C} sites has not been shown to play an important role in the stimulus effects of hallucinogenic agents. The potency of a series of antagonists to block the stimulus effects of LSD and (−)DOM in LSD-trained subjects strongly correlates with 5-HT_{2A} (r = + 0.75 and + 0.95, respectively) but not 5-HT_{2C} receptor affinity (Fiorella et al. 1995c). Quipazine and MK-212 have been demonstrated to possess partial agonist activity at both 5-HT_{2A} and 5-HT_{2C} receptors with respect to the stimulation of PI turnover (in vitro) (Conn and Sanders-Bush 1987). While this combination of receptor interactions might be expected to elicit hallucinations in humans, neither drug is hallucinogenic. The agonist activity of these compounds at 5-HT_{2C} receptors has also been demonstrated in vivo. MK-212 (Winter and Rabin 1993) and quipazine (Fiorella et al., unpublished data) fully substitute for the stimulus effects of the 5-HT_{2C} agonist *m*-chlorophenylpiperazine (Fiorella et al. 1995c). Thus, while 5-HT_{2C} and 5-HT_{2A} receptors may play an important role in the hallucinogenic effects of the phenethylamines and indolamines, it is doubtful that these interactions alone account for the ability of a given compound to elicit hallucinations in humans.

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