Characterization of the Discriminative Stimulus Produced by the Dopamine Antagonist Tiapride

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ABSTRACT
The ability of tiapride, a selective D2/D3 dopamine receptor antagonist, to exert discriminative stimulus control of responding was investigated by training rats to discriminate this drug (30 mg/kg) from saline in a two-lever, food-reinforcement procedure. Acquisition of tiapride discrimination required a relatively lengthy training period (mean of 76 sessions) but stable performance was maintained throughout the 18-month study. The dose of tiapride eliciting 50% tiapride-lever choice (ED50) was 2.2 mg/kg. After determination of the dose-effect curve for tiapride, substitution tests with several dopamine antagonists and other reference compounds were performed. All dopamine antagonists, including amisulpride (ED50 4 mg/kg), sulpiride (18 mg/kg), olanzapine (0.97 mg/kg), risperidone (0.22 mg/kg) and haloperidol (0.14 mg/kg), except clozapine (>10 mg/kg), produced dose-dependent substitution for tiapride. Tiapride-like stimulus effects were observed at doses that decreased response rates. However, ED50 values for substitution by tiapride, amisulpride, sulpiride, sulpropride, pimozide, clopabiprole and thioridazine were lower than ED50 values for decreasing responding. Additional studies were conducted to evaluate the ability of direct and indirect dopamine agonists to attenuate the tiapride discriminative stimulus. Pretreatment with d-amphetamine and nomifensine antagonized the discriminative stimulus effects of tiapride. Quinpirole, 7-OH-DPAT, bromocriptine and apomorphine partially blocked the stimulus effects of tiapride whereas SKF 38393 did not affect the discrimination. These results from substitution and antagonism tests indicated that the discriminative effects of tiapride are mediated by activity at D2/D3 dopamine receptors.

Drug discrimination procedures have been used successfully to characterize the pharmacological properties of many psychotropic drugs including opiates, psychomotor stimulants, anxiolytics and compounds acting through different neurotransmitter receptor subtypes. Through the use of appropriate tests of substitution for, and antagonism of, a training drug, it is possible, using drug discrimination, to make precise comparisons between different drugs and to investigate their mechanism of action.

The discriminative stimulus effects of directly (Colpaert et al., 1975; Appel et al., 1988; Sanger et al., 1997a) and indirectly (Colpaert et al., 1976a; Young and Glennon, 1986) acting dopamine agonists have been investigated in some detail. In contrast, there are only a few reports dealing with the stimulus effects of dopamine antagonists (Nielsen, 1993). Stewart (1962) trained rats to discriminate 4 mg/kg of chlorpromazine in a shock-escape procedure although Overton (1966) was unsuccessful in attempting to train rats to discriminate a slightly higher dose of this drug (5 mg/kg) in a T-maze. In lever pressing operant procedures three studies (Barry et al., 1974; Colpaert et al., 1976b; Goas and Boston, 1978) have found chlorpromazine to serve effectively as a discriminative stimulus and Goas and Boston (1978) also reported that chlorpromazine-induced stimulus control generalized to haloperidol. More recently, McElroy et al., (1989) trained rats to discriminate a dose of 0.05 mg/kg of haloperidol. The stimulus produced by this drug was dose-dependent and generalized fully to chlorpromazine.

These reports indicate that, under appropriate conditions, dopamine antagonists serve effectively as discriminative stimuli in rats. Our study was therefore carried out to investigate the discriminative stimulus effects of a dopamine antagonist in detail. The substance chosen as the training drug was the benzamide derivative tiapride, which is used clinically in the treatment of geriatric agitation, alcohol dependence and some forms of dyskinetic movement (Steele et al., 1993; Peters and Faulds, 1994). Unlike most dopamine antagonists that have affinities for other central neurotransmitter receptors, tiapride binds selectively to D2 and D3 dopamine receptors in vitro and in vivo (Jenner et al., 1978; Bischoff et al., 1982; Chivers et al., 1988). Tiapride blocks the behavioral effects of dopamine agonists (Jenner et al., 1978; 1993; Peters and Faulds, 1994). Unlike most dopamine antagonists that have affinities for other central neurotransmitter receptors, tiapride binds selectively to D2 and D3 dopamine receptors in vitro and in vivo (Jenner et al., 1978; Bischoff et al., 1982; Chivers et al., 1988). Tiapride blocks the behavioral effects of dopamine agonists (Jenner et al., 1978; 1993; Peters and Faulds, 1994). Unlike most dopamine antagonists that have affinities for other central neurotransmitter receptors, tiapride binds selectively to D2 and D3 dopamine receptors in vitro and in vivo (Jenner et al., 1978; Bischoff et al., 1982; Chivers et al., 1988). Tiapride blocks the behavioral effects of dopamine agonists (Jenner et al., 1978; 1993; Peters and Faulds, 1994).

ABBREVIATIONS: ED50, 50% effective dose; 7-OH-DPAT, 7-hydroxy-2-(di-n-propylamino)-tetralin; SKF 38393, (±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol.
Puech et al., 1978; Steele et al., 1993). It has not been reported to induce catalepsy, produces limited sedation and there is some evidence that it may act selectively on limbic structures (Jenner et al., 1978; Bischoff et al., 1982; Sanger et al., 1997b). Because of this pharmacological profile (i.e., receptor selectivity, limited sedation) tiapride was considered an appropriate compound for use in a drug discrimination procedure. In our study, rats were first trained to discriminate between tiapride and vehicle and then drug substitution experiments were conducted to compare various dopamine receptor antagonists and other reference compounds for their capacity to reproduce the tiapride cue. Additional studies were then conducted to evaluate the extent to which the stimulus effects of tiapride could be attenuated by pretreatment with direct and indirect dopamine agonists.

Methods

Subjects. Twenty-one male Wistar rats obtained from IFFA CREDO (L’Arbresle, France) were used. They weighed 180 to 200 g when obtained from the suppliers and were allowed to gain weight during the experiment so that by the end they weighed between 400 and 500 g. Animals were restricted to the food obtained during sessions and a daily ration of 15 to 20 g of standard laboratory food given at the end of each day and over the weekend. Housing was in individual cages under standard laboratory conditions with lights on between 7:00 A.M. and 7:00 P.M. Animals were housed and tested in accordance with current French legislation on animal experimentation.

Discrimination training. The method used for drug discrimination training was essentially that developed by Colpaert and co-workers (e.g., Colpaert et al., 1975). The animals were trained to press both levers in standard two-lever operant test chambers (MED-Associates, Inc. Georgia, VT) to obtain 45-mg food pellets (Noyes, formula P, Lancaster, NH). Only one lever was operational on any particular session. Initially, daily sessions were 30 min in duration and every lever press produced a pellet. The schedule requirement was then gradually increased until 10 lever presses were required for each pellet (fixed ratio 10: FR10). At this stage the daily session duration was reduced to 15 min and injections were started. Rats were given injections of either tiapride or physiological saline, 30 min before sessions, in the daily sequence SDDSDDSSDD (Drug drug S = saline). In some of the rats, responding on the right lever after drug injection and the left lever after saline injection was reinforced with food. For the other animals this relationship was reversed.

Initially, it was intended to attempt to train rats to discriminate a dose of tiapride that had little or no effect on rates of lever pressing. For 12 rats the initial training dose was therefore 10 mg/kg. After 17 sessions, however, it became apparent that the animals were not acquiring a discrimination and the dose was increased to 20 mg/kg and after a further 34 sessions to 30 mg/kg. Three rats from this group were dropped from the study after 30 to 45 sessions at the 30-mg/kg dose because of their particularly poor performance. With the other group of nine rats the training dose was 30 mg/kg from the beginning of discrimination training.

Drug testing. The training procedure was continued until the following criterion was met for a period of 10 successive days; the total number of responses on both levers before the first reinforcement was less than 15. When the criterion for successful discrimination control was reached, substitution and antagonism tests were carried out. During these tests the animal was placed in the test chamber at the appropriate time after injection and was reinforced after the first ratio of 10 responses had been completed on either lever. For the remaining of the 15-min session, responding on the lever on which the first 10 responses had occurred continued to be reinforced according to the FR10 schedule. Substitution tests were first carried out in each rat with several doses of tiapride before other drugs were tested. The tiapride dose-response function was also re-established approximately 18 mo later to investigate the possibility that tolerance or sensitization to the training drug had occurred.

Data analysis. The lever chosen and the total number of lever presses were recorded during each 15-min session. During tests of substitution and antagonism the results were expressed as the percentage of rats choosing the lever associated with the training dose of tiapride and the rate of responding expressed as a percentage of the rate on the preceding saline sessions. Drug effects on rates of lever pressing were analyzed statistically using Friedman analyses of variance followed by Wilcoxon matched-pairs signed-ranks tests. ED50 values for the potencies of different drugs to substitute for tiapride (i.e., doses at which 50% of rats tested chose the tiapride associated-lever) or to decrease rates of responding (i.e., doses that reduced response rates to 50% of control values) were calculated using log-probit analysis.

Drugs. The drugs used were tiapride hydrochloride, amisulpride, sulpiride, sulotropane, metoclopramide hydrochloride, raclopride, clozaprine maleate, remoxipride hydrochloride, haloperidol, clozapine, olanzapine, risperidone, chlorpromazine, thioridazine hydrochloride, pimozide, d-amphetamine sulfate, apomorphine hydrochloride, 7,8-DAT dopamine, bromocriptine mesylate, quinpirole hydrochloride, SKF 38393 hydrochloride, nomifensine maleate, ethanol, cocaine hydrochloride, morphine sulfate, diazepam, lorazepam and dixocilpine maleate. Raclopride was donated by Astra (Soder- talje, Sweden), risperidone by Janssen (Beerse, Belgium) and olan- zapine by Lilly (Indianapolis, IN). All other drugs were obtained from commercial sources or synthesized at Synthelabo Recherche.

All doses are expressed as the bases and injection volume was 1 or 2 ml/kg except for ethanol (13 ml/kg). Drugs were injected as solutions or suspensions in saline containing two drops of Tween 80. All injections were given i.p. 30 min before the start of the sessions except for amisulpride, sulpiride, sulotropane and pimozide (i.p., 60 min), ethanol (i.p., 10 min), cocaine (i.p., 15 min), apomorphine and morphine (s.c., 30 min).

Results

Effects of tiapride. For the 12 rats that began discrimination training at 10 mg/kg of tiapride, the discrimination was not acquired after 17 training sessions. The dose was then increased to 20 mg/kg and after a further 34 sessions to 30 mg/kg. Nine of these rats achieved the accuracy criterion after a further 18 to 64 training sessions. The other three rats were dropped from the experiment when it became apparent that they were not acquiring a discrimination. For the nine rats that began discrimination training at 30 mg/kg of tiapride, the mean number of sessions to criterion was 76 (range 42-149).

Figure 1 shows the results of the substitution tests with five tiapride doses (1, 3, 10, 30 and 60 mg/kg) after the discriminative criterion had been reached and when the tiapride dose-response curve was redetermined after a period of 18 mo had elapsed. Tiapride dose-effect curves were established in the same animals. Figure 1 shows that the sensitivity of the animals to the discriminative stimulus and response rate decreasing effects of tiapride changed very little throughout the study. Tiapride engendered dose-related increases in the percentage of rats selecting the drug-associated lever (fig. 1, top). The ED50 values for engendering tiapride lever responding after initial training and 18 mo later were 2.4 and 2.9 mg/kg, respectively. The ED50 values for the rate-decreasing effects of tiapride at the first and second determination were 32 and 36 mg/kg, respectively.
Effects of dopamine antagonists. Several dopamine antagonists were evaluated for their capacity to reproduce the discriminative stimulus of tiapride. Figure 2 shows results for benzamide drugs, results for other dopamine antagonists are shown in figure 3. ED50 values for the dose-response curves are presented in table 1.

As shown in figure 2, all benzamide drugs produced dose-related increases in the percentage of rats selecting the tiapride-associated lever. Clebopride, sulpiride, amisulpride and sulpiride produced full substitution for tiapride. Raclopride, metoclopramide and remoxipride produced a maximum of approximately 80% responding on the tiapride-associated lever at doses that gave rise to substantial reductions in rates of lever pressing.

As shown in figure 3, several other dopamine antagonists produced dose-related substitution for tiapride, including haloperidol, risperidone, chlorpromazine and thioridazine. Olanzapine and pimozide also produced responding predominantly on the tiapride-associated lever whereas clozapine produced responding on the saline-associated lever.

Based on the ED50 values for engendering tiapride-associated lever responding and for reducing response rate (table 1), the dopamine antagonists can be classified as drugs that substitute for tiapride with ED50 values lower than those required to decrease response rate (ratio < 1) and drugs that substitute for tiapride with ED50 values higher than those necessary to decrease response rate (ratio > 1). The rank order was as follows: tiapride > amisulpride > sulpiride > sulpiride > pimozide > clebopride ≥ thioridazine ≥ olanzapine = chlorpromazine > raclopride ≥ metoclopramide ≥ risperidone ≥ haloperidol ≥ remoxipride.

Fig. 1. Effects of tiapride after initial training and 18 mo later (same rats). Data represent the percentage of rats selecting the tiapride-associated lever and the rates of responding expressed as a percentage of control rates obtained from the sessions preceding the test sessions. Points are means ± S.E.M. based on 13 rats. *P < .01 compared to saline control values.

Fig. 2. Effects of benzamide dopamine antagonists in rats trained to discriminate tiapride (30 mg/kg) from saline. Data represent the percentage of rats selecting the tiapride-associated lever and the rates of responding expressed as a percentage of control rates obtained from the sessions preceding the test sessions. Points are means ± S.E.M. based on 6 to 8 rats except for tiapride where n = 18. *P < .05; **P < .01 compared to saline control values.
Effects of other reference compounds. Several reference compounds, including an opioid agonist (morphine), a dopamine agonist (apomorphine), a dopamine reuptake inhibitor (cocaine), a NMDA antagonist (dizocilpine), two benzodiazepines (diazepam and lorazepam) and ethanol were evaluated for tiapride-like discriminative stimulus effects (table 2). Ethanol was the only drug tested to produce more than 50% selection of the tiapride-associated lever.

Effects of pretreatment with dopamine agonists. Several direct and indirect dopamine agonists were evaluated for their ability to attenuate the stimulus effects of tiapride. As shown in figure 4, pretreatment with the indirect dopamine agonists, d-amphetamine and nomifensine, dose-dependently antagonized the stimulus effect of the training dose of tiapride. The dopamine agonists, quinpirole, 7-OH-DPAT, bromocriptine and apomorphine, partially blocked the stimulus effect of the training dose of tiapride whereas the D1 dopamine agonist, SKF 38393, did not antagonize the discriminative stimulus effects of tiapride (fig. 4, top). The rate-decreasing effects of the dopamine agonists in combination with tiapride prevented testing of higher doses (fig. 4, bottom).

Administration of a fixed dose of d-amphetamine (0.03 or 0.1 mg/kg) in combination with several doses of tiapride (30-60 and 100 mg/kg) resulted in a rightward shift in the

TABLE 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED50 (mg/kg)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiapride</td>
<td>2.2 (1.2–3.8)</td>
<td>41 (ND&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>4 (2.1–7.6)</td>
<td>24 (17–35)</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>18 (5.4–33)</td>
<td>74 (48–203)</td>
</tr>
<tr>
<td>Sultopride</td>
<td>1.5 (0.6–3.2)</td>
<td>4.5 (2.6–9.8)</td>
</tr>
<tr>
<td>Raclopride</td>
<td>0.13 (0.14–0.19)</td>
<td>0.81</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>1.4 (0.69–5)</td>
<td>1.1 (ND)</td>
</tr>
<tr>
<td>Remoxipride</td>
<td>4.8 (2.1–18)</td>
<td>2.6 (2.3–3)</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2.7 (ND)</td>
<td>4.3 (ND)</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>3.4 (1.5–14)</td>
<td>4.1 (ND)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.97 (0.54–2.9)</td>
<td>0.93 (0.84–1)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>&gt;10 (ND)</td>
<td>4.8 (ND)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1.9 (ND)</td>
<td>1</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.22 (0.14–0.28)</td>
<td>0.16 (0.14–0.18)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.14 (0.11–0.17)</td>
<td>0.09 (0.074–0.10)</td>
</tr>
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</table>

Data are ED50 (95% confidence interval) based on six to eight rats, except for tiapride (<i>n</i> = 18). The ratio is the ED50 for substitution divided by ED50 for decreasing response rates.

<sup>a</sup> ND, Not determined.

TABLE 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>n/N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Percent tiapride lever</th>
<th>Percent control rate (± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>4</td>
<td>6/6</td>
<td>0</td>
<td>115 (±13)</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>0.03</td>
<td>5/5</td>
<td>0</td>
<td>81 (±12)</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>6/6</td>
<td>0</td>
<td>70 (±13)</td>
</tr>
<tr>
<td>Ethanol</td>
<td>250</td>
<td>8/8</td>
<td>13</td>
<td>99 (±14)</td>
</tr>
<tr>
<td>Dizocilpine</td>
<td>0.025</td>
<td>8/8</td>
<td>13</td>
<td>104 (±16)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1</td>
<td>8/8</td>
<td>13</td>
<td>118 (±10)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.1</td>
<td>6/6</td>
<td>33</td>
<td>93 (±15)</td>
</tr>
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</table>

<sup>a</sup> n/N, Number of rats responding at least 10 times on one of the levers/number of rats tested whose data are included in mean response rate.

<sup>b</sup> P < .05.

<sup>c</sup> P < .01 difference from control.

Fig. 3. Effects of nonbenzamide dopamine antagonists in rats trained to discriminate tiapride (30 mg/kg) from saline. Data represent the percentage of rats selecting the tiapride-associated lever and the rates of responding expressed as a percentage of control rates obtained from the sessions preceding the test sessions. Points are means ± S.E.M. based on six to eight rats. *<i>P</i> < .05; **<i>P</i> < .01 compared to saline control values.

with tiapride prevented testing of higher doses (fig. 4, bottom).
tiapride substitution dose-response curve (fig. 5, top) indicating surmountable antagonism. The ED50 value for engendering tiapride lever responding was increased 16- and 50-fold after pretreatment with 0.03 and 0.1 mg/kg d-amphetamine.

Discussion

Several previous studies reported that training animals to discriminate dopamine antagonists, such as haloperidol and chlorpromazine, was difficult, and it was hypothesized that the general depressant effects of the drugs and/or the long duration of action of haloperidol may have impaired the acquisition of the discrimination (Stewart, 1962; Barry et al., 1974; Colpaert et al., 1976b; Goas and Boston, 1978; McElroy et al., 1989). As tiapride has been reported to have dopamine antagonist activity with relatively limited depressant effects (Steele et al., 1993), it was chosen as the training drug in our study, in the hope that it would provide a more discriminable stimulus than other dopamine antagonists. The results of our study show that tiapride produces a discriminative stimulus that can reliably control responding in rats. Similar to results with other discriminable drugs, tiapride engendered dose-dependent increases in the percentage of rats selecting the drug-associated lever and the rates of responding expressed as a percentage of control rates obtained from the sessions preceding the test sessions. Further, it retained this ability over the 18-mo period covered by the study with no differences between the initial and last dose-effect curves. However, as previously observed with haloperidol and chlorpromazine, tiapride required a relatively lengthy training period (mean of 76 sessions) to function as a discriminative stimulus.

Evidence from previous research has showed that chlor-
promazine and haloperidol cross-generalized and that the indirect dopamine agonists amphetamine and cocaine blocked the haloperidol discriminative stimulus, suggesting that the discriminative stimulus effects of haloperidol are mediated by dopamine receptors (Goas and Boston, 1978; McElroy et al., 1989); however, only a limited number of dopaminergic and nondopaminergic drugs were tested in these studies. In our study, we investigated a number of reference compounds for their capacity to reproduce or to antagonize the discriminative stimulus of tiapride. Results indicate that $D_2/D_3$ dopamine receptors mediate the discriminative stimulus effects of tiapride. First, several dopamine antagonists substituted for the discriminative stimulus effect of tiapride. Second, several nondopaminergic drugs produced responding predominantly on the saline-associated lever. Finally, direct $D_2/D_3$ but not $D_1$ dopamine agonists reduced and indirect dopamine agonists blocked the discriminative stimulus effects of tiapride.

The dopamine antagonists examined in substitution tests included benzamide (tiapride, amisulpride, sulpiride, sultopride, clebopride, raclopride, metoclopramide and remoxipride) and nonbenzamide (clozapine, olanzapine, pimozide, haloperidol, thioridazine, chlorpromazine, risperidone) derivatives. All dopamine antagonists, except clozapine, fully or partially (averaging a maximum substitution of about 70%) produced dose-related increases in the percentage of rats selecting the tiapride-associated lever. The lack of substitution by clozapine is consistent with previous findings that clozapine itself produces discriminative stimulus effects that are not mediated by dopaminergic mechanisms but are related to cholinergic muscarinic antagonism and 5HT$_2$ receptor blockade (Goas and Boston, 1978; Browne and Koe, 1982; Nielsen, 1988; Hoenicke et al., 1992, Wiley and Porter, 1992). It is of interest that olanzapine, which structurally and pharmacologically resembles clozapine and has been found to substitute for clozapine (Moore et al., 1992), produced partial substitution for tiapride. Although both clozapine and olanzapine show affinities for muscarinic, adrenergic, histamine and serotonin receptors, olanzapine exhibits higher affinity for $D_2$ dopamine receptors than clozapine (Ashby and Wang, 1996; Bymaster et al., 1996).

Tiapride-like stimulus effects of dopamine antagonists were observed at doses that markedly reduced rates of responding. The question thus arises as to whether drugs substitute for tiapride on the basis of their rate-decreasing effects. To examine further the pharmacological specificity of tiapride discrimination, several reference compounds were evaluated for tiapride-like discriminative stimulus effects (table 2). The finding that drugs such as morphine and lorazepam did not substitute for tiapride at doses that decreased rate of responding indicates that the discriminative stimulus effects of tiapride are not mediated by nonspecific depressant effects. The pharmacological specificity of tiapride discrimination is further supported by the finding that ethanol was the only drug tested to produce more than 50% selection of the tiapride-associated lever. In addition to its action at GABA$_A$ and NMDA receptors, ethanol also interacts with other transmitters including dopamine (Deitrich et al., 1989; Grant, 1994). Specifically, ethanol stimulates dopamine release in terminal dopaminergic areas (Di Chiara and Imperato, 1988). However, morphine and cocaine which also increase extracellular dopamine concentrations (Di Chiara and Imperato, 1988) did not substitute for tiapride in our study. The mechanism of the partial substitution obtained with ethanol is, thus, not clear, although it is tempting to speculate that it may be related to the therapeutic efficacy of tiapride in the management of alcohol abuse (Steele et al., 1993; Peters and Faulds, 1994; Shaw et al., 1994). Studies were conducted to evaluate the ability of several direct and indirect dopamine agonists to attenuate the stimulus effects of tiapride. The nonselective dopamine agonist, apomorphine, and the $D_2/D_3$ dopamine agonists, quinpirole, 7-OH-DPAT and bromocriptine (Sokoloff et al., 1990; Levesque et al., 1992), partially blocked the stimulus effect of the training dose of tiapride. In contrast, the $D_1$ dopamine agonist, SKF 38393 (Arnt et al., 1992), did not affect the discrimination. These findings provide support for a $D_2/D_3$ dopamine receptor mediation of tiapride discrimination. Although none of these drugs produced full antagonism, their depressant effects on rate of responding prevented testing of higher doses.

The indirect dopamine agonists, d-amphetamine and nomifensine, dose-dependently antagonized the discriminative stimulus effects of tiapride. The doses required to antagonize the discriminative stimulus effects of tiapride were, however, much lower than those necessary to produce direct behavioral effects in rats (Colpaert et al., 1979). The reasons for this sensitivity of the tiapride discrimination to antagonism by the indirect dopamine agonists are not clear. It is possible that chronic treatment with tiapride had produced supersensitivity of dopamine receptors although the dose-response curves established to tiapride itself showed no evidence that either sensitization or tolerance had developed to the effects of tiapride.

$D_2/D_3$ dopamine receptors are thought to serve as both postsynaptic receptors and presynaptic (auto)receptors that can control dopamine synthesis and release. In our study, all dopamine antagonists substituted for tiapride at doses that have been shown to antagonize apomorphine-induced effects (hyperactivity) mediated by postsynaptic receptors (Costall and Naylor 1975; Puech et al., 1978; Purralt et al., 1997). This is particularly true for the few dopamine antagonists (amisulpride, sulpiride) that discriminate between pre- and postsynaptic dopamine receptors (Costall et al., 1980; Puech et al., 1981; Purralt et al., 1997; Schoemaker et al., 1997). Drugs that increase extracellular dopamine concentrations, including morphine and cocaine, failed to engender tiapride-like discriminative effects and, in contrast, d-amphetamine and nomifensine blocked the tiapride cue, further suggesting that dopamine release induced by presynaptic activity of tiapride does not participate in its interoceptive cue. These findings suggest that presynaptic dopamine antagonism does not play an important role in the discriminative stimulus effects of tiapride and indicate that blockade of postsynaptic $D_2/D_3$ dopamine receptors is sufficient to create an interoceptive discriminative stimulus.

Based on the $ED_{50}$ values shown in table 1, dopamine antagonists can be classified according to their substitution to response-reduction dose ratio. Tiapride (0.054), amisulpride (0.17), sulpiride (0.24), sultopride (0.33), pimozide (0.63), clebopride (0.81) and thioridazine (0.83) substituted for the discriminative stimulus effects of tiapride at doses lower than those required to decrease response rate (ratio < 1). Olanzapine and chlorpromazine produced a tiapride-like
discriminative stimulus at doses that reduced responding (ratio = 1). Raclopride (1.2), metoclopramide (1.3), risperidone (1.4), haloperidol (1.6) and remoxipride (1.8) generalized to tiapride only at doses that disrupted lever-pressing performance (ratio > 1).

It appears from our results, and previously published data, that drugs which displayed tiapride-like discriminative effects with an ED$_{50}$ about 3 to 20 times lower than the ED$_{50}$ that drugs which displayed tiapride-like discriminative performance (ratio, edged to tiapride only at doses that disrupted lever-pressing done (1.4), haloperidol (1.6) and remoxipride (1.8) general-

sulpiride and sultopride, display limbic selectivity as re-

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