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Validation of the tremulous jaw movement model for assessment of the motor effects of typical and atypical antipsychotics: effects of pimozide (Orap) in rats

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Abstract

Drug-induced tremulous jaw movements (TJMs) in rats have been used as a model of parkinsonian tremor. Previous studies demonstrated that the typical antipsychotic haloperidol induced TJMs after acute or subchronic administration, while atypical antipsychotics did not. Moreover, it has been suggested that the relative potency for suppression of tacrine-induced TJMs relative to the suppression of lever pressing can be used to discriminate between typical and atypical antipsychotics. In order to validate this model with additional drugs, the present studies assessed the effects of the typical antipsychotic pimozide. In the first series of experiments, the effects of acute pimozide on tacrine-induced TJMs and lever pressing were examined. As with haloperidol, pimozide failed to suppress tacrine-induced TJMs, even at doses considerably higher than those that suppressed lever pressing. In the second group of experiments, rats were given single daily injections of pimozide (0.125–1.0 mg/kg) or tartaric acid vehicle for 13 days, and were observed for TJMs on days 1, 7, and 13. Pimozide induced TJMs in a dose-related manner on all days. The jaw movements occurred largely in the 3–7 Hz frequency range characteristic of parkinsonian tremor. These data support the hypothesis that typical antipsychotics can induce TJMs in rats, and demonstrate that chronic administration of typical antipsychotics is not necessary for induction of TJMs. TJMs induced by acute or subchronic pimozide may be related to early-onset motor syndromes such as drug-induced parkinsonism.

Keywords: Schizophrenia; Extrapyramidal; Tacrine; Cognex; Tremor; Parkinson

1. Introduction

Antipsychotic drugs are thought to exert their therapeutic effects primarily by blocking dopamine (DA) D_2 family receptors in mesolimbic and mesocortical areas of the brain (Creese et al., 1976; Dixon et al., 1995; Farde et al., 1988, 1989, 1992; Kapur and Remington, 2001; Kapur and Seeman, 2001; Lidlow, 2000; Seeman, 1992, 2002; Seeman et al., 1976). The therapeutic potencies of antipsychotic drugs directly correlate with their affinities for the D_2 receptor (Creese et al., 1976; Seeman and Lee, 1975; Seeman et al., 1976). However, "typical" antipsychotic drugs such as phenothiazines (e.g., chlorpromazine) and butyrophenones (e.g., haloperidol) also induce early-onset motor side effects such as akinesia and tremor and, when administered chronically, they induce tardive dyskinesia (Casey, 2004; Gerlach and Casey, 1988; Tarsy, 1983). In contrast, newer "atypical" antipsychotics such as clozapine and quetiapine are much less prone to induce these motor side effects (Casey, 1989, 2004; Geddes et al., 2000; Hippus, 1989; Leucht et al., 1999; Meltzer, 1989), despite the fact that these compounds also block D_2 receptors (Kapur et al., 1999; Nordstrom et al., 1995, 1998). Moreover, not only is clozapine less likely to induce motor side effects, but it has also been shown to ameliorate motor dysfunctions in patients with idiopathic Parkinson's disease (Bernardi and Del Zompo, 1990; Factor and Friedman, 1997; Fisher et al., 1990; Friedman and Lannon, 1990;

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Pakkenberg and Pakkenberg, 1986). Various neurochemical hypotheses have been proposed to explain these unique motor properties of atypical antipsychotics (Kapur and Remington, 2001; Kapur and Seeman, 2001; Meltzer, 1989; Meltzer et al., 2003; Olney and Farber, 1994, 1995a,b; Roth et al., 1995; Schotte et al., 1996; Seeman, 2002; Seeman et al., 1997; Svensson et al., 1995; Van Tol et al., 1991; Wadenberg et al., 2001; Wilson et al., 1998; Wong and Van Tol, 2003).

While the exact neurochemical mechanisms underlying the distinction between typical and atypical antipsychotics are yet to be elucidated, various behavioral procedures have been used to compare the effects of typical antipsychotic drugs with those of atypical antipsychotics (e.g., Gunne et al., 1986; Hoffman and Donovan, 1995; Moore et al., 1992, 1997; Stanford and Fowler, 1997; Wiley et al., 1994; Salamone et al., 1998; Wadenberg et al., 2001). For example, considerable research has focused upon tests involving induction of catalepsy and suppression of conditioned avoidance responding (see review by Wadenberg et al., 2001). Another animal model employed to investigate the motor effects of typical and atypical antipsychotic drugs is drug-induced tremulous jaw movements (TJMs; also known as vacuous jaw movements or purposeless chewing) in rodents. TJMs are defined as vertical deflections of the lower jaw that resemble chewing, but are not directed at any particular stimulus (Salamone et al., 1998). It has been shown that TJMs can be induced by acute or subchronic administration of the typical antipsychotic drug haloperidol (Correa et al., 2004; Diana et al., 1992; Egan et al., 1996b; Rupniak et al., 1983, 1985, 1986; Steinpreis and Salamone, 1993; Steinpreis et al., 1993, 1996, 1997, 1998; Trevitt et al., 1997, 1998; Wisniecki et al., 2003). TJMs can be produced by other means of interfering with DA transmission, such as acute administration of the monoamine depleting agent reserpine (Baskin and Salamone, 1993; Steinpreis and Salamone, 1993; Salamone and Baskin, 1996) and striatal DA depletions (Jicha and Salamone, 1991; Finn et al., 1997; Rodriguez Diaz et al., 2001). TJMs are also induced by cholinomimetic drugs such as muscarinic agonists (e.g., pilocarpine; Baskin et al., 1994; Rupniak et al., 1983, 1985; Salamone et al., 1986, 1990; Stewart et al., 1987, 1988) and anticholinesterases (e.g., physostigmine and tacrine; Collins et al., 1993; Kelley et al., 1989; Carriero et al., 1997; Mayorga et al., 1997). Considerable evidence indicates that drug-induced TJMs show many of the characteristics of parkinsonian tremor in humans (Cousins et al., 1997; Cousins and Salamone, 1998; Egan et al., 1996b; Finn et al., 1997; Jicha and Salamone, 1991; Salamone and Baskin, 1996; Salamone et al., 1990, 1998; Steinpreis et al., 1993). For example, the interactions between acetylcholine and DA that have been observed in TJMs (see Salamone et al., 1998 for review) are similar to the pharmacological characteristics of human parkinsonism (Duvoisin, 1967; Harbaugh et al., 1984; Marsden et al., 1975; Noring et al., 1984; Tarsy, 1983; Weiss et al., 1980). It has also been shown that tacrine-induced TJMs can be attenuated by antiparkinsonian drugs, including L-dopa, apomorphine, bromocriptine, amantadine, benztropine, pergolide, and ropinirole (Cousins et al., 1997; Salamone et al., 2005). Finally, TJMs display a peak frequency in the 3–7 Hz range (Cousins and Salamone, 1998; Finn et al., 1997; Mayorga et al., 1997; Salamone and Baskin, 1996), which is similar to the frequency range reported for parkinsonian tremor (Adams and Victor, 1981).

Although the typical antipsychotic drug haloperidol induces TJMs in rats (Correa et al., 2004; Diana et al., 1992; Egan et al., 1996b; Rupniak et al., 1983, 1985, 1986; Steinpreis and Salamone, 1993; Steinpreis et al., 1993, 1996, 1997, 1998; Trevitt et al., 1997, 1998; Wisniecki et al., 2003), atypical antipsychotics such as clozapine, olanzapine, and quetiapine not only fail to induce TJMs when administered alone (Betz et al., in press; Gunne et al., 1986; Johansson et al., 1986; Steinpreis et al., 1997; Trevitt et al., 1997, 1999; Marchese et al., 2002), but in fact they suppress cholinomimetic-induced TJMs (Betz et al., in press; Chesler and Salamone, 1996; Trevitt et al., 1997, 1998, 1999). It has also been shown that DA antagonists, including antipsychotic drugs, suppress operant lever pressing on various schedules of reinforcement (Beninger et al., 1987; Salamone, 1987, 1992; Salamone et al., 1991, 1996; Sanger and Perrault, 1995; Wiley et al., 1994). Accordingly, suppression of lever pressing is considered to be a reliable dose-dependent effect of virtually every antipsychotic agent. It has been suggested that the ratio of the ED_{50} for suppression of tacrine-induced jaw movements relative to the ED_{50} for suppression of lever pressing on a fixed-ratio 5 (FR 5) schedule could be used as an index of liability of an antipsychotic drug to produce motor side effects (Betz et al., in press; Salamone et al., 1998; Trevitt et al., 1997, 1998, 1999). For example, haloperidol, when administered acutely, failed to suppress tacrine-induced jaw movements in doses up to 1.0 mg/kg, while it produced dose-dependent suppression of lever pressing with an ED_{50} value of 0.088 mg/kg, thereby yielding an ED_{50} ratio value larger than 11.36 (Trevitt et al., 1997). In contrast, the atypical antipsychotics clozapine, olanzapine, and quetiapine reduced tacrine-induced TJMs at relatively low doses compared to those required for suppression of lever pressing, with all of them having ED_{50} ratios less than 1 (Betz et al., in press; Trevitt et al., 1997, 1999).

In order to test further the validity of the TJM model for assessing the motor effects of antipsychotic drugs, it is necessary to assess the effects of additional typical antipsychotics. Pimozide (Orap), a diphenylbutylpiperidine, is a typical antipsychotic drug that has a high-affinity for DA receptors with moderate D_2 selectivity, and the drug has been shown to be clinically effective in treating

schizophrenia and some delusional disorders (Chouinard and Annable, 1982; Feinberg et al., 1988; Sultana and McMonagle, 2000; Tueth and Cheong, 1993; van Kammen et al., 1987) as well as Tourette's syndrome (Bruggeman et al., 2001; Jimenez-Jimenez and Garcia-Ruiz, 2001; Shapiro et al., 1987; Tueth and Cheong, 1993). Most importantly for the present study, pimozide has been shown to produce motor side effects, including tremor, in patients with schizophrenia (Chouinard and Annable, 1982; Claveria et al., 1975; Sultana and McMonagle, 2000), and to exacerbate motor symptoms in patients with Parkinson's disease (Tarsy et al., 1975). In the present experiments, the effects of pimozide on jaw movements and lever pressing were examined in order to determine if pimozide would show a profile of motor effects similar to that of haloperidol. The first series of experiments (experiments 1 and 2) examined the effects of acute administration of pimozide on tacrine-induced jaw movements and on operant lever pressing on an FR 5 schedule to determine the relative potency of the drug for these effects. Previously, pimozide has been shown to fail to reduce TJMs induced by the muscarinic agonist pilocarpine (Stewart et al., 1988), while this drug has been shown to suppress lever pressing on fixed-ratio schedules (Fowler et al., 1986; Wiley et al., 1994). Thus, it was expected that pimozide would fail to suppress tacrine-induced TJMs even at doses much higher than those required for suppression of lever pressing. In experiment 3, pimozide was administered daily to rats for 13 consecutive days, and animals were observed on days 1, 7, and 13 of drug treatment in order to assess the ability of pimozide to induce jaw movements. Previous work using similar procedures demonstrated that haloperidol induced jaw movements within the first 2 weeks of administration (Steinpreis and Salamone, 1993; Trevitt et al., 1998). In addition, freeze-frame analyses of videotapes of pimozide-treated animals were used to determine the local frequency of pimozide-induced TJMs (experiment 4). It was hypothesized that pimozide would show a profile of behavioral effects that would resemble that of haloperidol on these tasks.

2. Materials and methods

2.1. Subjects

A total of 64 male Sprague Dawley rats (Harlan Sprague Dawley, Indianapolis, IN) with no prior drug experience were used in the present experiments. The animals were 315–450 g during the course of the experiment and had *ad libitum* access to laboratory chow and water (except for the food deprivation in the operant experiment). Animals were group-housed in a colony that was maintained at approximately 23 °C and had a 12-h light/dark cycle (lights on at 07:00 h). These studies were conducted according to University of Connecticut and NIH guidelines for animal care and use.

2.2. Drugs

Tacrine and pimozide were purchased from Sigma Aldrich Chemical (St. Louis, MO). Pimozide was dissolved in warm 0.3% tartaric acid, which also served as the vehicle control. Tacrine was dissolved in 0.9% saline. The drug dosages were selected based upon previous published reports (Stewart et al., 1988; Trevitt et al., 1997, 1998) and pilot work.

2.3. Experimental procedures: tremulous jaw movements

Observations of rats took place in a 30×30×30 cm clear Plexiglas chamber with a wire mesh floor, which was elevated 42 cm from the bottom of the table top. This allowed for the viewing of the animal from several angles. TJMs were defined as rapid vertical deflections of the lower jaw that resembled chewing but were not directed at any particular stimulus (Salamone et al., 1998). Each individual deflection of the jaw was recorded using a mechanical hand counter by a trained observer, who was blind to the experimental condition of the animal being observed. Separate studies with two observers demonstrated an inter-rater reliability of r=0.92 (p<0.05) using these methods.

2.4. Experimental procedures: operant lever pressing

Animals were food-deprived to 85% of their free-feeding body weight. Behavioral tests were performed in 28×23×23 cm experimental chambers (Med Associates, St. Albans, VT) containing one lever that was located on the left side of the front panel. Animals were initially trained to press on a continuous reinforcement schedule for 45 mg food pellets (Bioserve, Frenchtown, NJ) for 1 week, and then were shifted to a fixed-ratio 5 (FR5) schedule (30-min sessions, 5 days a week, for at least 4 weeks). Drug testing began 1 week after animals had reached acceptable baseline levels (1200 or more lever presses per session for three consecutive sessions).

2.5. Experiments

2.5.1. Experiment 1: effects of acute pimozide on tacrine-induced TJMs

A group of 16 rats was used to assess the effects of acute pimozide injections on tacrine-induced jaw movements. Animals were tested once a week for 5 weeks. On test days each animal received an injection of 5.0 mg/kg tacrine 10 min before testing to induce TJMs, as well as a dose of pimozide or vehicle 4 h before testing. The following doses of pimozide were used: tartaric acid vehicle, 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.50

mg/kg, and 1.0 mg/kg. Each rat received all doses in a randomly varied order, with one injection per week. All drugs were administered via intraperitoneal (IP) injection. Rats were placed in the observation chamber immediately after tacrine injection for a 10-min habituation, after which they were observed for 5 min by a blind observer (i.e., the observation period was 10–15 min after tacrine injection).

2.5.2. Experiment 2: effect of acute pimozide on operant lever pressing

A group of 9 rats was used to examine the effects of acute pimozide administration on lever pressing on an FR5 schedule. Drug testing was performed on consecutive Fridays between 15:00 and 19:00 h. The following doses of pimozide were administered via IP injection 4 h before testing: tartaric acid vehicle, 0.125 mg/kg, 0.25 mg/kg, 0.50 mg/kg, and 1.0 mg/kg. Each rat received all doses in a randomly varied order, with one injection per week. Baseline (i.e., non-drug) behavioral testing on the FR5 schedule was continued on Monday to Thursday of each week.

2.5.3. Experiment 3: effect of repeated pimozide on the induction of TJMs

Separate groups of rats were used to test each dose of pimozide. Rats received daily IP injections for 14 days of one of the following conditions (n=9–10 per dose): tartaric acid vehicle, 0.25 mg/kg, 0.50 mg/kg, and 1.0 mg/kg pimozide. Each animal received an injection of a particular dose of pimozide or vehicle for 13 consecutive days, and the animals were tested on days 1, 7, and 13 for the induction of jaw movements. On test days, rats were given an IP injection of pimozide or vehicle 4 h before testing and then returned to their home cage. After 3 h and 50 min, the animals were removed from the home cage and placed in a Plexiglas observation chamber and allowed to habituate for 10 min. After the end of the habituation period, the animals were observed by a blind observer for 5 min, during which time each jaw movement was recorded with a mechanical hand counter.

2.5.4. Experiment 4: videotape analysis of local frequency of pimozide-induced TJMs

Two additional rats received repeated daily injections of 1.0 mg/kg pimozide, as described above, for 9 days. On day 10, these rats were injected with pimozide, placed in the observation chamber 4 h later, and were videotaped over a 20-min period. The sections of these videotapes that allowed for clear observation of the orofacial region were then subjected to a freeze-frame analysis (1 frame=1/30 s), in which the observer went frame-by-frame through each burst of jaw movements (i.e., each group of at least two jaw movements that were within 1.0 s of each other). The observer recorded the inter-movement interval for each jaw movement within these bursts, which was defined as the number of frames between each point of maximal jaw opening shown during successive jaw movements.

2.6. Data analysis

The behavioral data for experiments 1 and 2 were analyzed using a repeated-measures analysis of variance (ANOVA), with dose as the repeated measure. Planned comparisons using the overall error term were used to assess the differences between each dose and the control condition, which kept the total number of comparisons to the number of conditions minus one (Keppel, 1982; pp. 106–124). The ED_{50} for each drug effect was estimated by using curvilinear regression analysis (GraphPad Prism), which employed an exponential decay function. This method was used to provide confidence intervals as well as ED_{50} estimates. Data from the tests on days 1, 7, and 13 were analyzed separately using a one-way ANOVA with dose as the between-subjects factor. Planned comparisons using the overall error term were used to assess the differences between each dose and the control condition for each day.

3. Results

3.1. Experiments 1 and 2: effects of acute pimozide on tacrine-induced TJMs and lever pressing

As shown in Fig. 1, acute administration of pimozide had no significant effect on tacrine-induced tremulous jaw movements within the dose range used (0.0625–1.0 mg/kg) $F(5, 75)=1.123$, n.s.. However, as seen in Fig. 2, acute administration of pimozide led to dose-related decreases in

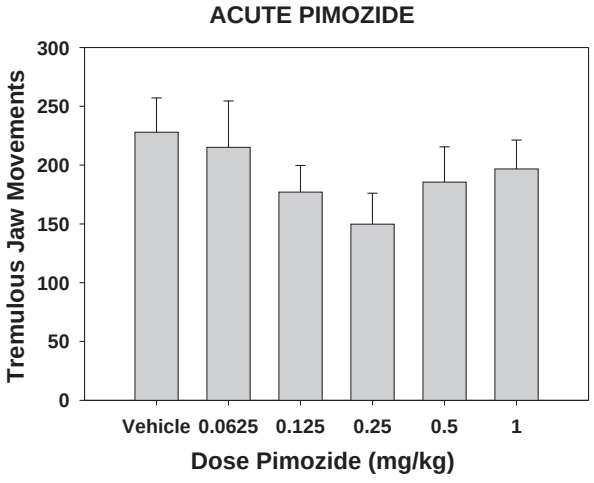

Fig. 1. The effects of acute pimozide on tacrine-induced tremulous jaw movements. Mean (±S.E.M.) numbers of tremulous jaw movements (per 5 min) recorded after injections of 5.0 mg/kg tacrine plus tartaric acid (vehicle) and tacrine plus different doses of pimozide are shown. Pimozide had no significant effect on tacrine-induced tremulous jaw movements.

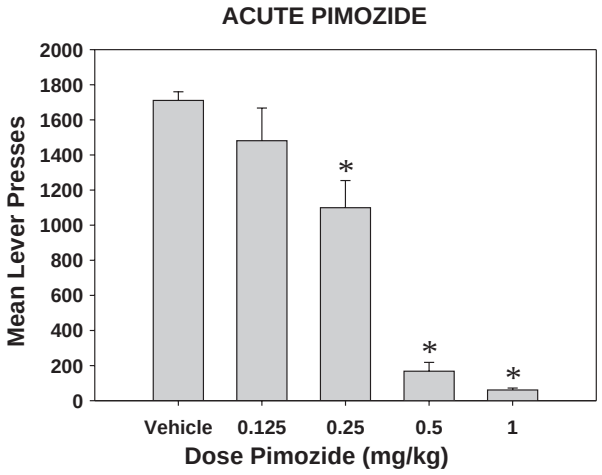

Fig. 2. The effects of acute pimozide on lever pressing on an FR 5 schedule are shown. Mean (±S.E.M.) number of lever presses (per 30 min) after administration of vehicle and different doses of pimozide. Pimozide significantly attenuated lever pressing in a dose-dependent manner (*differed from vehicle: $p<0.05$).

lever pressing, which were statistically significant $F(4, 32)=41.198$, $p<0.001$. Planned comparisons revealed that the highest three doses (i.e., 0.25, 0.5, and 1.0 mg/kg) of pimozide was significantly different from vehicle ($p<0.05$). The ED_{50} for the suppression of lever pressing by pimozide was estimated to be 0.2721 mg/kg, with 95% confidence intervals of 0.3668–0.2163 mg/kg. Table 1 shows the ED_{50} values for the suppression of tacrine-induced TJMs and lever pressing by pimozide in experiments 1 and 2, as well as the ratio of these ED_{50} values (i.e., ED_{50} for suppression of jaw movements divided by ED_{50} for suppression of lever pressing). The ED_{50} values and their ratios for haloperidol, clozapine, fluphenazine, olanzapine, risperidone, thioridazine, and quetiapine, which were obtained using the same acute administration procedure as in the present studies, are also listed in Table 1 for comparison (Betz et al., in press; Salamone et al., 1998; Trevitt et al., 1997, 1999).

Table 1
ED_{50} values (mg/kg) for the behavioral effects of acute typical and atypical antipsychotic drugs

Compound	ED_{50} (mg/kg)		
	TJM	LP	TJM/LP ratio
Haloperidol	>1.0	0.088	>11.36
Pimozide	>1.0	0.2721	>3.68
Fluphenazine	0.39	0.16	2.44
Thioridazine	9.90	6.58	1.50
Risperidone	0.061	0.063	0.97
Clozapine	3.32	5.43	0.61
Olanzapine	0.40	1.12	0.36
Quetiapine	7.223	21.4	0.34

Behavioral data for compounds other than pimozide are taken from Betz et al. (in press), Salamone et al. (1998), and Trevitt et al. (1997, 1999) (TJM: suppression of tacrine-induced tremulous jaw movements; LP: suppression of lever pressing).

3.2. Experiment 3: effect of repeated pimozide on the induction of TJMs

As depicted in Fig. 3, repeated administration of pimozide led to a significant induction of jaw movement activity for all three test days (i.e., day 1, day 7, and day 13). A one-way ANOVA on the data from day 1 revealed a significant effect of dose $F(3, 36)=5.986$, $p<0.005$ with the group that received the highest dose displaying a significantly larger number of TJMs than control ($p<0.005$). For the day 7 test, there was also a significant effect of dose $F(3, 36)=7.346$, $p<0.005$, and the groups that received 1.0 mg/kg and 0.5 mg/kg doses displayed significantly larger numbers of jaw movements than the vehicle group ($p<0.001$ and $p<0.05$, respectively). On day 13, there was again a significant effect of dose $F(3, 36)=6.299$, $p<0.005$, and the group that received 1.0 mg/kg significantly differed from the vehicle control ($p<0.001$).

3.3. Experiment 4: videotape analysis of local frequency of pimozide-induced TJMs

Fig. 4 displays the results of the freeze-frame analyses of videotaped samples of pimozide-induced jaw movement activity. A total of 64 jaw movements within bursts were analyzed. Data are shown as the number of inter-movement intervals within each time category. To interpret these data in terms of frequencies (i.e., jaw movements per second), frequencies were calculated as the reciprocal of the inter-movement interval (e.g., 5/30 s corresponds to 6 Hz, 6/30 s to 5 Hz, etc.). As shown in Fig. 4, the vast majority (87.5%) of the jaw movement activity within bursts took place in the

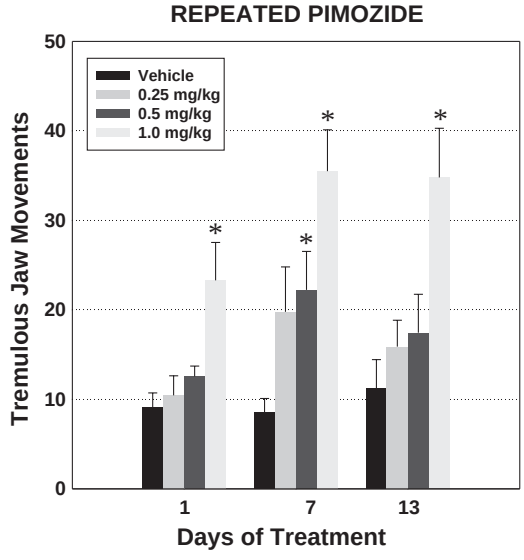

Fig. 3. The effects of repeated administration of pimozide on the induction of tremulous jaw movements are shown. Mean (±S.E.M.) number of tremulous jaw movements (per 5 min) produced by each dose of pimozide (or vehicle) on days 1, 7, and 13 of drug treatment are depicted. There were significant main effects of dose and day (* differed from vehicle: $p<0.05$).

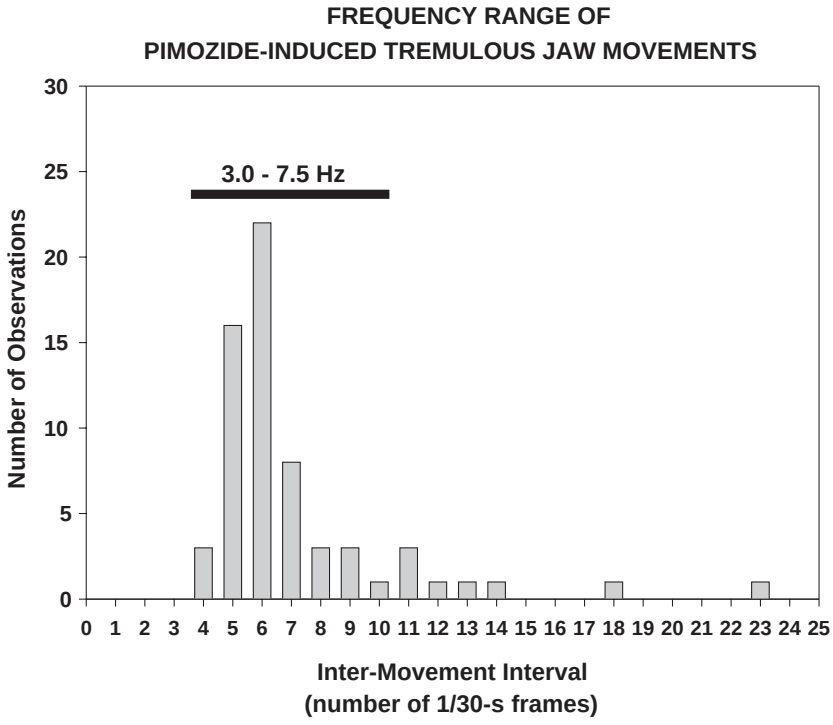

Fig. 4. This figure shows the results of the freeze-frame analysis of inter-movement intervals for pimozide-induced TJMs in two representative rats. Distribution of the total number of inter-movement intervals within each time bin is depicted. Bar indicates the inter-movement intervals that correspond to the 3.0–7.5 Hz frequency range. Peak frequency was in the 5–6 Hz frequency range (i.e., 5/30–6/30 s inter-movement times).

3.0–7.5 Hz frequency range, with a marked peak in the 5–6 Hz range.

4. Discussion

It was demonstrated in experiment 1 that acute administration of pimozide failed to suppress tacrine-induced TJMs within the dose range that was used (0.0625–1.0 mg/kg). This finding is consistent with Stewart et al. (1988), who showed that pimozide (1.0 mg/kg subcutaneous) failed to suppress the jaw movements induced by the muscarinic agonist pilocarpine (4.0 mg/kg IP). The present results are also in line with the profile of another typical antipsychotic drug, haloperidol, which was shown to have no significant effect on tacrine-induced TJMs in doses up to 1.0 mg/kg when administered acutely (Trevitt et al., 1997) or subchronically for 14 days (Trevitt et al., 1998). The results of experiment 2 showed that acute administration of pimozide resulted in a significant dose-dependent reduction in the number of FR5 lever presses, with an estimated ED_{50} value of 0.2721 mg/kg. Past research has indicated that the ratio of the ED_{50} for suppression of tacrine-induced TJMs relative to the ED_{50} for suppression of lever pressing can be used as an index of liability of an antipsychotic drug for inducing motor side effects (Betz et al., in press; Salamone et al., 1998; Trevitt et al., 1997, 1998, 1999). The results of experiments 1 and 2 indicate that the ratio of ED_{50} values for pimozide had a value greater than 3.68 (see Table 1). Previous work from our laboratory using the same acute administration procedure has shown that the typical antipsychotic drug haloperidol did not suppress tacrine-induced jaw movements even at doses up to 11 times the ED_{50} for suppression of lever pressing. In contrast, atypical antipsychotic drugs such as clozapine, olanzapine, and quetiapine all suppressed tacrine-induced TJMs and exhibited ED_{50} ratio values smaller than 1, as also shown in Table 1 (Betz et al., in press; Trevitt et al., 1997, 1999). The rank order of the ED_{50} ratios shown in Table 1 appears to correspond well with the clinical data on the rank order of motor side effect liability for these antipsychotic compounds. The typical antipsychotics pimozide and haloperidol have been shown to have high liability for production of motor side effects, while the atypical antipsychotics clozapine, quetiapine and olanzapine are less likely to produce motor side effects (Claveria et al., 1975; Chouinard and Annable, 1982; Bezchlibnyk-Butler and Remington, 1994; Casey, 1997; Sultana and McMonagle, 2000; Tarsy et al., 2002). Thus, the results of experiments 1 and 2 demonstrate that the profile of behavioral effects of pimozide on tacrine-induced TJMs and lever pressing is similar to that of haloperidol, while it is substantially different from those of the atypical antipsychotics clozapine, olanzapine, and quetiapine. The present results also support the hypothesis that the ED_{50} ratio can be used as an index of motor side effect liability for various antipsychotic compounds.

It was demonstrated in experiment 3 that repeated administration of pimozide induced significant jaw movement activity in a dose-related manner on days 1, 7, and 13. Even after the first administration, 1.0 mg/kg pimozide induced significant jaw movement activity, and the effects became more pronounced on day 7, with 0.5 and 1.0 mg/kg producing significantly more jaw movements than vehicle. On all days, the highest dose (1.0 mg/kg) of pimozide induced significantly larger numbers of jaw movements than the vehicle control. These data are in line with previous research showing that TJMs can be induced by both acute and subchronic (1–4 weeks) administration haloperidol (Correa et al., 2004; Diana et al., 1992; Egan et al., 1996b; Rupniak et al., 1983, 1985, 1986; Steinpreis and Salamone, 1993; Steinpreis et al., 1993, 1996, 1997, 1998; Trevitt et al., 1998; Wisniecki et al., 2003). The level of TJM activity induced by pimozide in the present study was very robust for a DA antagonist and was, if anything, slightly higher than the 22–28 jaw movements per 5 min that typically are induced by haloperidol in our laboratory (Trevitt et al., 1998; Correa et al., 2004; Wisniecki et al., 2003). In addition to pimozide and haloperidol, the selective D_2 antagonist raclopride also has been shown to induce TJMs after repeated subchronic administration (Steinpreis et al., 1996). In contrast, several studies that have examined the effects of atypical antipsychotics have found little or no jaw movement activity in response to injections of clozapine, olanzapine, and quetiapine (Betz et al., in press; Gunne et al., 1986; Johansson et al., 1986; Steinpreis et al., 1997; Trevitt et al., 1997, 1999; Marchese et al., 2002). These data, together with the results of experiment 3, indicate that acute or subchronic administration of typical antipsychotics can reliably induce TJMs in rats.

Although previous studies have reported induction of jaw movements after acute or subchronic administration of haloperidol, there are other studies in which jaw movement activity was observed after chronic (6–12 months) treatment with haloperidol (e.g., Egan et al., 1996b; Waddington, 1990; Waddington and Molloy, 1987). Consequently, it has been a matter of controversy whether neuroleptic-induced jaw movements are a model of early-onset motor effects such as parkinsonian tremor (Rupniak et al., 1985, 1986; Salamone et al., 1998) or whether they are a model of late-onset tardive dyskinesia (Ellison and See, 1989; See and Ellison, 1990a). This issue has been complicated by the fact that various factors, such as method of assessment, dose, and route and schedule of drug administration, appear to influence types of jaw movement activity induced by haloperidol (Egan et al., 1996a,b; See and Ellison, 1990b; Turrone et al., 2002). Route and schedule of administration are of relevance to the validity of the jaw movement model, given that most patients with schizophrenia take their medication daily via the oral route. In many studies using haloperidol decanoate injections, jaw movements were observed only after long-term treatment with the drug (e.g., Egan et al., 1995; Gunne et al., 1982; Hyde et al., 1995; Mithani et al., 1987; Stoessl et al., 1989), while haloperidol appears to induce jaw movements very rapidly when administered orally (e.g., Glenthoj and Hemmingsen, 1989; Rupniak et al., 1983, 1985) or via IP injection (e.g., Glassman and Glassman, 1980; Rupniak et al., 1986; Steinpreis et al., 1993, 1997, 1998; Steinpreis and Salamone, 1993; Trevitt et al., 1998; Wisniecki et al., 2003). Moreover, several studies have shown differential effects of continuous vs. intermittent treatment with haloperidol on jaw movement activity, although the data from these studies are somewhat conflicting, possibly due to methodological differences (Glenthoj, 1993; Glenthoj and Hemmingsen, 1989; Glenthoj et al., 1990; Sant and Ellison, 1984; See and Ellison, 1990b; Turrone et al., 2003; see Turrone et al., 2002 for review). Despite these complications, however, some evidence suggests that early-onset and late-onset jaw movements may have distinct pharmacological profiles and neurochemical substrates (Egan et al., 1996b). While tardive jaw movements are suppressed with increased doses of haloperidol, early-onset jaw movements are not (Egan et al., 1996b). In addition, anticholinergic drugs such as scopolamine and atropine have been shown to attenuate early-onset TJMs (Rupniak et al., 1985; Steinpreis et al., 1993), but a few studies have indicated that late-onset jaw movements are not suppressed by scopolamine (Glenthoj, 1993; Sakai et al., 2001). Recent data from our laboratory indicate that the jaw movements induced by subchronic administration of pimozide are suppressed by the muscarinic antagonist tropicamide (Betz et al., 2004). Given that early-onset and late-onset jaw movements may be pharmacologically and neurochemically distinct, it is unlikely that early-onset TJMs, such as those induced by pimozide in the present studies, are closely related to tardive dyskinesia for several reasons. First, one of the essential features of tardive dyskinesia is its delayed onset by months to years after the initial neuroleptic treatment (APA Task Force, 1992; Gerlach and Casey, 1988), but early-onset jaw movements are observed within minutes to hours of the initial drug treatment. This time course is very brief even if the relatively short lifespan of the rat is taken into consideration. In the present studies, 1.0 mg/kg of pimozide induced significant jaw movement activity even on day 1, only 4 h after the first drug administration. Secondly, as mentioned above, early-onset TJMs induced by haloperidol are suppressed by antiparkinsonian anticholinergic drugs (Rupniak et al., 1985; Steinpreis et al., 1993). In contrast, tardive dyskinesia is actually exacerbated by anticholinergic drugs and can even be ameliorated by cholinomimetics (Burnett et al., 1980; Fahn et al., 1974). Thirdly, TJMs induced by DA depletion or cholinomimetics display the peak frequency range of 3–7 Hz (Cousins and Salamone, 1998; Finn et al., 1997; Mayorga et al., 1997; Salamone and Baskin, 1996), while tardive dyskinesia usually occurs in the frequency range of 1–2 Hz (Alpert et al., 1976; Wirshing et al., 1989, 1991). In the present study, we demonstrated that pimozide-

induced jaw movements also tend to occur in the 3–7 Hz frequency range, with the peak frequency in the vicinity of 5–6 Hz. Taken together, these observations support the use of TJMs induced by acute or subchronic IP administration of neuroleptics as a model of early-onset motor side effects such as drug-induced parkinsonism.

The neurochemical mechanisms that underlie the distinction between typical and atypical antipsychotics remain uncertain. It has been suggested that the D_4 antagonist effects of clozapine and other atypical antipsychotics are related to the unique clinical characteristics of this class of compounds (Seeman, 1992; Seeman et al., 1997). More recently, Kapur and Seeman (2001) proposed that variations in the rate of dissociation from the DA D_2 receptor across different drugs may be a useful marker for differentiating typical from atypical antipsychotics. Wadenberg et al. (2001) reported that in vivo D_2 receptor occupancy is highly correlated with potency for producing catalepsy and suppressing avoidance responding, which are two behavioral markers of motor side effect liability. It also is possible that actions on other neurotransmitters contribute to the motor characteristics of typical and atypical antipsychotics. Clozapine and olanzapine have been shown to bind to muscarinic acetylcholine receptors (Miller and Hiley, 1974; Richelson and Souder, 2000; Schotte et al., 1996; Snyder et al., 1974). This observation is relevant to studies of TJMs because cholinomimetic-induced TJMs can be blocked muscarinic antagonists such as scopolamine, atropine, benztropine, methoctramine, telenzepine or pirenzepine, and reduced by knockout of M_4 muscarinic receptors (Cousins et al., 1997; Mayorga et al., 1997, 1999; Rupniak et al., 1983; Salamone et al., 2001). The ability of atypical antipsychotics to bind to 5-HT receptors also has been suggested to be related to the clinical characteristics of these drugs (e.g., Meltzer, 1989, 2003). Roth et al. (1995) hypothesized that the ratio of $5\text{-HT}_{2A}/D_2$ binding is useful for distinguishing between typical and atypical antipsychotics. Several studies of TJM activity support the hypothesis that cholinergic and serotonergic systems interact in the regulation of motor function (Betz et al., in press; Carlson et al., 2003a,b; Stewart et al., 1987, 1988; Trevitt et al., 1997). Additional research will be necessary to determine if D_2 occupancy, actions on other receptors, or a combination of these effects provides the neurochemical explanation for the distinction between typical and atypical antipsychotics.

The present results, together with those of Trevitt et al. (1997, 1998), have demonstrated that pimozide and haloperidol have similar profiles in terms of their behavioral effects. Both pimozide and haloperidol are DA D_2 family antagonists (Freedman et al., 1994). Animal studies have also shown that both haloperidol and pimozide reduce locomotor activity and produce catalepsy (Correa et al., 2004; Drinkenburg et al., 1999; Ezrin-Waters and Seeman, 1977; Fujiwara, 1992; Hoffman and Donovan, 1995; Karolewicz et al., 1996; Sousa et al., 2001; Spivak and Amit, 1986; Wadenberg et al., 2001). Both haloperidol (Drinkenburg et al., 1999; Salamone et al., 1991, 1996; Sanger and Perrault, 1995; Trevitt et al., 1997, 1998) and pimozide (Beninger et al., 1987; Fowler et al., 1986; Porter and Villanueva, 1988; Wiley et al., 1994) have been shown to suppress operant lever pressing. Human clinical studies have shown that both drugs are effective in treating symptoms of schizophrenia (Angst et al., 1989; Chouinard and Annable, 1982; Feinberg et al., 1988; Joy et al., 2001; Sultana and McMonagle, 2000; Tueth and Cheong, 1993; van Kammen et al., 1987). Both haloperidol (Carlson et al., 2003a,b; Moleman et al., 1982; Tran et al., 1997; Yen et al., 2004) and pimozide (Chouinard and Annable, 1982; Claveria et al., 1975; Sultana and McMonagle, 2000) have a high liability for producing motor side effects in human patients. Moreover, pimozide has been reported to be more likely to produce parkinsonian tremor compared to other typical agents (Sultana and McMonagle, 2000). This clinical report is consistent with the present finding that pimozide induces a robust TJM response in rats. These observations suggest that assessment of TJM activity may be useful for characterizing novel compounds in terms of their potential typical or atypical antipsychotic profile. Additional research with pimozide may advance our understanding of how early-onset motor effects such as tremor are generated by typical antipsychotics, and may help to elucidate the basal ganglia mechanisms involved in the induction of parkinsonian symptoms.

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