Neuroleptic-induced vacuous chewing movements as an animal model of tardive dyskinesia: a study in three rat strains

C.A. Tamminga, J.M. Dale, L. Goodman, H. Kaneda, and N. Kaneda
Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, Baltimore, MD 21228, USA

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Abstract. Vacuous chewing movements (VCMs) in three different rat strains developed at considerably different rates after 19 weeks of continual haloperidol treatment at an average daily dose of 1.5 mg/kg. Sprague Dawley (SD) rats displayed relatively high rates of VCMs with low variability, compared to Wistar (W) and Long Evan (LE) rats. Atropine decreased but did not abolish VCMs in two of the three strains (LE > SD). After haloperidol withdrawal, VCMs remitted gradually in all strains, but least rapidly in the SD rats. In a separate group of SD rats, VCMs were rated weekly from the start of haloperidol treatment and showed considerable interindividual variability. Even after 24 weeks of continuous haloperidol, 12 out of 32 treated rats showed no VCMs at all, while 13 out of 32 had intense movements, analogous to the clinical situation in which only some patients treated with neuroleptics develop tardive dyskinesia. These results indicate that there are individual and strain differences in the development of VCMs, and suggest that there may also be genetically determined differences in the development of tardive dyskinesia.

Key words: Animal model – Tardive dyskinesia – Chronic haloperidol – Rat strains – Neuroleptic

Neuroleptic drugs are frequently administered clinically for the long-term treatment of psychotic disorders. Their administration has been associated with a delayed-onset hyperkinetic movement disorder called tardive dyskinesia (TD) which is characterized by involuntary movements of the mouth, extremities and trunk (Klawans and Rubovits 1974; Tarsy and Baldessarini 1974). The syndrome is a significant clinical problem because of its frequency (Kane et al. 1985), its occasional intensity and its medical-legal implications. While the etiologic agent of TD is generally taken to be chronic neuroleptic treatment, the pathophysiology is less clear. Many investigators suppose that chronic blockade of dopamine receptors, resulting in dopamine receptor supersensitivity, is the mechanism of the motor disorder or is a critical component of the pathophysiology (Clow et al. 1980; Rupniak 1984). Other investigators have proposed additional or alternative hypotheses, involving GABA, D1/D2 receptor imbalance, or cholinergic or peptidergic systems (Jeste and Wyatt 1980; Thaker et al. 1987). More specific information about the pathophysiology of tardive dyskinesia might lead to the development of drugs for psychosis which do not induce TD. In addition, knowledge about the pathophysiology of TD might lead to strategies for preventing the syndrome in patients who require continual neuroleptic treatment. A rodent model of the syndrome as used in the present study might greatly facilitate the investigation of these possibilities.

Rats treated chronically with neuroleptic drugs often develop spontaneous mouth movements (Clow 1980; Iversen et al. 1980; Gunne et al. 1982; Waddington et al. 1982; Mithani et al. 1987). Such movements have been described as “vacuous chewing movements” (VCMs), and reliable techniques have been described to rate them (Gunne et al. 1982; Waddington et al. 1982). There is disagreement in the literature about the similarities of these movements to tardive dyskinesia and its validity as an animal model of TD. The characteristics of TD to be approximated by an animal model of the syndrome would include: 1) irregular, purposeless, but continual movements of the oral region, extremities, or trunk, 2) delayed development of these movements after prolonged neuroleptic dosing, with a protracted course after drug cessation, 3) antagonism by dopamine receptor antagonists, 4) resistance to suppression with anticholinergic treatments, and 5) exacerbation by stress or activity. The conclusions of different investigators are not entirely consistent with respect to susceptibility, movement type or severity, and movement duration after withdrawal. Thus, there remains a question about the utility of these drug-induced VCMs as a rodent model of TD.

Because of the variability among reports of VCMs in
chronically neuroleptic-treated rats, we investigated strain susceptibility as a factor in these differences. We studied the onset of VCMs in male rats from three different strains, Sprague-Dawley, Long-Evans, and Wistar, and found that differences between strains were evident in their motor responses to prolonged oral administration of haloperidol.

**Methods**

**Animals.** Rats from three different strains, Sprague-Dawley (SD), (N=13), Long-Evans (LE), (N=12), and Wistar (W), (N=12), were given either haloperidol (1.5 mg/kg/day) or tap water in their cage drinking water. At the beginning of the experiment, animals of all strains weighed 296–358 g and were all aged 56–65 days; weight and age overlapped entirely in the three strains. Rats were housed in groups of three or four, separated by strain, on a 12 h light-dark cycle, at a constant room temperature of 21°C. Treatment of the three strains continued for 20 weeks. Initially the animals were given a drinking water solution with 16 mg haloperidol/liter water; water consumption was monitored per species and dosage adjustments were made when necessary to achieve a daily haloperidol dose of 1.5 mg/kg/day (range: 1.13–2.28 mg/kg/day). In our laboratory, this dose resulted in plasma levels of haloperidol for SD of 3.9 ng/ml, for LE of 3.9 ng/ml, and for W of 6.7 ng/ml. Plasma for these assays was obtained from pooled trunk blood from four treated animals in each species. There was no strain difference in haloperidol dose administered. Rat chow was unlimited and similar in all groups. Animals receiving haloperidol had an average 15% slower weight gain over 20 weeks (SD = 19%; LE = 5.5%; W = 20%), and drank approximately 20% less water (SD = 33%; LE = 15%; W = 35%) than the control rats.

Haloperidol was analyzed using a modification of the Bianchetti and Morselli (1978) assay using gas-liquid chromatography and nitrogen-phosphorous detection, operating in the nitrogen mode.

**Behavioral ratings.** Rats from the three different strains were observed weekly for vacuous chewing movements from the 10th through the 19th week of treatment, although treatment continued for 20 weeks. Animals were transferred individually to a small Plexiglass cage (20 x 30 x 23 cm) which was completely empty. The cage was placed on a revolving platform in the center of the rating room to enable the rater to keep the animal’s mouth in view. The animal was allowed to accommodate for 4–5 min in the cage. Then the rater, blind to drug condition, counted and recorded the number of jaw movements during four sequential 30-s counting periods; the count stopped whenever grooming began and restarted when grooming stopped. All movements were quantified by experienced raters kept unaware of the animal’s treatment. Two types of movements were recorded: discrete vacuous chewing movements and bursts of rapid jaw movements. For calculation, each burst of rapid jaw movement was counted as equivalent to two VCMs. This method was described previously by Guine et al. (1982). A separate group of SD rats were treated as described with haloperidol or water for 24 weeks with behavioral ratings done weekly from the onset of treatment. For comparison between haloperidol and control groups and between different rat strains, the nonparametric Mann-Whitney U-statistic was used with the Bonferroni correction.

**Pharmacologic challenges.** After 19 weeks of continuous haloperidol or water treatment, all animals from the three strains were challenged with atropine sulfate, 5 mg/kg, IP. VCMs were rated blindly as described above at 0, 30, and 60 min after atropine. Comparison between rat strains in their response to atropine was done using two-way ANOVA (strain x time).

After 20 weeks of continuous treatment with haloperidol, the drug treatment was stopped and all three rat strains were given normal drinking water. Thereafter, rats were rated individually (by raters blind to the previous treatment condition) twice weekly for the next 2 weeks. The disappearance of the VCMs was quantified and compared between groups using two-way ANOVA with trend analysis.

**Results**

VCMs developed in all three rat strains in the haloperidol-treated animals. The difference in VCM rate between the treatment and the control groups in each strain was significant. (Table 1). Long-Evans (LE) rats had the highest VCM rates after 19 weeks of haloperidol treatment but also the highest baseline rates and the lowest drug/placebo ratio; Wistar (W) rats showed the second largest drug/placebo value, and the Sprague-Dawley (SD) rats demonstrated the largest drug/placebo ratio in VCM rates (Fig. 1). After 19 weeks of treatment, all rats were challenged with atropine sulfate (5 mg/kg) in a single IP administration. The average maximum response of the VCMs in the drug-treated group to a single administration of atropine (greater after 30 then

<table>
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<th>Strain</th>
<th>Haloperidol</th>
<th>Water</th>
<th>K-W</th>
<th>df</th>
<th>F</th>
</tr>
</thead>
<tbody>
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<td>Sprague-Dawley</td>
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<td>1.3 (0.35)</td>
<td>7.00</td>
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<tr>
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<td>8.4 (1.30)</td>
<td>7.71</td>
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</tr>
<tr>
<td>Wistar</td>
<td>15.4 (1.13)</td>
<td>2.5 (0.73)</td>
<td>6.25</td>
<td>1</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Fig. 1.** VCM rates in three different rat strains during weeks 10–19 of oral haloperidol treatment. Both basal and drug-induced rates of VCMs differed between strains. VCM rates in the drug-treated group significantly exceeded the control group in each strain (P < 0.02). — Controls; ---- Haldol