High frequency oral movements induced by long-term administration of amperozide but not FG5803 in rats

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Abstract Long-term studies of antipsychotic-induced oral movements may serve as a rat model of acute and tardive movement disorders. Vacuous chewing movements (VCM), tongue protrusions (TP), and jaw tremors (TR) were studied in rats during acute and chronic administration of two potential antipsychotics, amperozide and FG5803. Comparisons were made with haloperidol and vehicle. Single intraperitoneal injections of amperozide (0.2, 1, or 5 mg/kg) or FG5803 (1.2, 6, or 30 mg/kg) were without effect on oral behaviors. During long-term drug administration, withdrawal and readministration, endpoint analysis was focused on changes in supranormal oral movements. The maximal mean control frequencies found at 29 sessions during 14 months experiment +2 standard deviations were used to define the upper limit of the normal range. FG5803 (1.2, 6, or 30 mg/kg per day) administered via the drinking water for 12 months, did not produce significant deviations from this normal range with respect to VCM, TP, or TR, and this drug was not studied further. Rats receiving amperozide (0.2, 1, or 5 mg/kg per day) showed dose-related increases in oral movements over the year. The changes began after 3 months of treatment with amperozide 1 and 5 mg/kg per day, but became statistically significant only during the second half of the treatment year. Amperozide 0.2 mg/kg per day did not produce significant changes in oral movements during administration for a year, but drug withdrawal resulted in a significant rise in TP behavior. Haloperidol (1 mg/kg per day) produced increases in supranormal oral movements which tended to level out after 9 months. In all groups with significant elevations (i.e. haloperidol and amperozide 1 and 5 mg/kg per day), there was a persistence of such movements during a month of drug withdrawal. During treatment with amperozide (1 or 5 mg/kg per day), some rats developed a high frequency chewing behavior up to 175 VCMs/min. It is concluded that long-term treatment with amperozide, but not FG5803, produced a tardive pattern of supranormal oral movements. The importance of these findings for the clinical future of amperozide is difficult to predict, due to the unexpected finding of high-frequency chewing, which has not been noticed before during extensive studies of classical neuroleptics.

Key words Amperozide • FG5803 • Haloperidol • Antipsychotics • Oral movements • Chronic administration • Acute administration • Acute dystonia • Tardive dyskinesia • Extrapyramidal side effects • Rat

Introduction

The clinical use of classical neuroleptics is associated with a variety of motor disturbances, such as acute dystonia (AD), parkinsonism, akathisia and tardive dyskinesia (TD) (Sovner and Dimascio 1978; Casey 1987). TD is particularly feared as it persists long after drug discontinuation and may become irreversible in some patients afflicted (Jeste and Wyatt 1982; Schooler and Cane 1982; Casey 1987). Consequently, there is a great need of an instrument to monitor the inherent risk of adverse effects related to the extrapyramidal motor system in new antipsychotic drugs before they are marketed. In attempts to predict neuroleptic-induced movement disorders, numerous investigations of effects of long-term neuroleptic administration in rats have been performed and several rodent models have been proposed (see Waddington 1990 for review).
Rats chronically exposed to classical neuroleptics display an enhancement of spontaneous oral movements, including non-object directed chewing, referred to as vacuous chewing movements (VCM), jaw tremors (TR) and tongue protrusions (TP). These increased oral movement frequencies have been reported to develop gradually during long-term neuroleptic administration and to persist after drug withdrawal (Gunne et al. 1982, 1986; Gunne and Häggström 1983; Waddington 1983; Sant and Ellison 1984; Mithani et al. 1987). In contrast, clozapine and melperone, compounds with low extrapyramidal side effect liability, did not induce these behaviors (Gunne et al. 1986; Johansson et al. 1986; Gunne and Johansson 1989). Therefore, measurement of neuroleptic-induced VCM frequencies in rats has been proposed as a rat model of TD (Gunne et al. 1982; Gunne and Häggström 1983; Waddington 1983; Sant and Ellison 1984; Mithani et al. 1987). However, other investigators have reported an early appearance of increased levels of chewing and no persistence of the behaviors after drug withdrawal (Rupniak et al. 1983, 1986; Glenthøj and Hemmingson 1989). Consequently, Rupniak et al. (1986) suggested that neuroleptic-induced chewing may resemble AD rather than TD. However, this discussion may be of less importance, since drugs which elicit AD are known to induce TD as well in susceptible individuals (Kane et al. 1986; Keepers and Casey 1991).

The neurochemical mechanisms behind neuroleptic-induced oral movements are not fully understood. Most likely, alterations in dopamine (DA) transmission play an important role, since all clinically effective neuroleptics are known to be potent blockers of DA receptors (Carlsson 1988; Meltzer et al. 1989; Deutch et al. 1991). In addition, interference with several other transmitter systems affects oral movements in rats. For instance, 5-hydroxytryptamine (5-HT) agonists increased vacuous chewing in rats after systemic (Stewart et al. 1989) or intranigral administration (Liminga et al. 1993). Furthermore, systemic or intrastriatal administration of cholinergic agonists has been reported to induce non-object directed chewing behaviors of high intensity (Gunne et al. 1982; Rupniak et al. 1983; Salamone et al. 1990).

Amperozide and FG5803 are two newly developed compounds with potential antipsychotic action (Christensson 1992). The chemical structure of amperozide contains a diphenylbutyl and a 1-piperazinecarboxamide residue (Christensson 1992). Amperozide shows a low affinity for dopamine D₁ and D₂, muscarinic and 5-HT₁A-receptors, but is a potent 5-HT₂ blocker (Meltzer et al. 1989; Svartengren and Simonsson 1990). Furthermore, amperozide has been found to inhibit reuptake of DA, 5-HT and noradrenaline (Haskins et al. 1987; Eriksson 1990). FG5803 is a 1-piperazinecarboxamide, the chemical structure of which is related to amperozide, and contains a butyrophenone residue. However, its pharmacological profile differs from antipsychotic butyrophenones, for instance by not being cataleptogenic and showing very weak effects on apomorphine-induced stereotypies (Christensson 1992). FG5803 is also a 5-HT₂ receptor blocker, with a low affinity for dopamine D₂ receptors (Christensson 1992).

The present study was carried out in order to determine if chronic administration of amperozide or FG5803 would affect rat oral behaviors. An increase in oral movements, particularly if it develops after a time lag (tardive) and remains persistent during drug discontinuation, may signal TD-related problems when the drugs are introduced in the clinic.

### Materials and methods

This study was performed according to the standards of Good Laboratory Practice regulations (GLP 1978).

#### Animals

Sprague-Dawley rats (ALAB AB, Sollentuna, Sweden) were housed under standardized conditions (mean room temperature 22 ± 2°C, relative humidity from 25 to 65%, light on from 7 a.m. to 7 p.m.) and given commercial rat food ad lib. There were four animals to each cage, unless reduced by mortality.

#### Behavioral observations

The rats were individually placed in a Plexiglas cage (2 x 3 x 4 dm) with a mirror to improve visibility. After a 2-min habituation period, the number of oral behaviors observed during a 2-min period were recorded. The recorded behaviors were: vacuous chewing movements (VCM) referring to non-object directed quick openings and closings of the mouth in the vertical plane, bursts of tremor in the masseter muscle (jaw tremors, TR) and non-object directed protrusion of the tongue (TP). VCM may occur isolated or in episodes of several repetitive openings and closings of the mouth, occasionally accompanied by TP. TR represent alternate oral behaviors and do not occur together with VCM and tongue protrusions. After a burst of jaw tremors (teeth chattering) there are often a few VCMs. During neuroleptic administration all these behaviors are known to increase.

#### Acute study

A total number of 72 rats (mean body weight ± SD of 240 ± 35 g) were randomly divided into nine groups (n = 8, four of each sex). They received a single intraperitoneal (IP) injection of either the vehicle saline (two groups; control 1 was run in parallel with haloperidol and amperozide treatment and control 2 in parallel with FG5803), the reference compound haloperidol (Haldol, Janssen Pharmaceutica, Belgium) 2 mg/kg, amperozide (Pharmacia LEO Therapeutics AB, Sweden) 0.2, 1, 5 mg/kg or FG5803 (Pharmacia LEO Therapeutics AB, Sweden) 1.2, 6, 30 mg/kg. Injection volumes were 0.2–0.5 ml. Behavioral observations were performed before the injection (baseline), at 1, 3, 5, 8 and 24 h and 2, 3, 5 and 8 days after the injection.