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Cholinergic Manipulation of Perioral Behaviour Induced by Chronic Neuroleptic Administration to Rats

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Abstract. Rats treated continuously for 4 months with haloperidol (1.4–1.6 mg/kg/day), trifluoperazine (4.5–5.1 mg/kg/day), or sulpiride (102–110 mg/kg/day), but not clozapine (23–26 mg/kg/day), exhibited an increased frequency of chewing jaw movements. Chewing in both control and haloperidol-treated rats was increased by acute administration of the cholinergic agents pilocarpine or physostigmine. Physostigmine or pilocarpine also induced abnormal gaping jaw movements; physostigmine-induced gaping was more prevalent in haloperidol-treated rats than control rats receiving physostigmine alone.

Acute administration of the anticholinergic agents scopolamine and atropine decreased chewing in control animals and reduced haloperidol-induced chewing to control values or below. The effects of these cholinergic manipulations suggest that neuroleptic-induced perioral responses in rats do not resemble tardive dyskinesia in man.

Key words: Neuroleptics – Perioral responses – Cholinergic agents – Tardive dyskinesia – Acute dystonic reactions – Rat

The administration of neuroleptic drugs to schizophrenic patients for several months or years is associated with the development of drug-induced tardive dyskinesia (see Marsden et al. 1975). The most characteristic feature of this condition is the emergence of orofacial dyskinesias, including tongue protrusion and chewing jaw movements. Tardive dyskinesias often appear during drug administration, but may first become apparent on drug withdrawal or reduction of dosage. The movements may persist following withdrawal from neuroleptic treatment and, in some cases, may be permanent. The development of tardive dyskinesia has been attributed to ensuing dopaminergic overactivity as a consequence of chronic neuroleptic treatment (Klawans 1973). Tardive dyskinesias can be alleviated by drugs which acutely antagonise central dopaminergic function, and are exacerbated or made manifest by administration of anticholinergic agents, such as scopolamine (see Kazamatsuri et al. 1972; Baldessarini and Tarsy 1978; MacKay and Sheppard 1979; Jenner and Marsden 1982). In contrast, the cholinergic agonist physostigmine may reduce neuroleptic-induced tardive dyskinesia.

There have been numerous attempts to establish an animal model of tardive dyskinesia. In primates undergoing chronic neuroleptic treatment, abnormal movements occur which resemble human tardive dyskinesia (Weiss et al. 1977; Gunne and Barany 1976, 1979; McKinney et al. 1980). Chronic treatment of rats with neuroleptics, such as thioridazine, trifluoperazine, fluphenazine, haloperidol, and *cis*-flupenthixol, produces orofacial movements which mainly take the form of purposeless chewing jaw movements (Sahakian et al. 1976; Clow et al. 1979; Howells and Iversen 1979; Waddington and Gamble 1980; Waddington et al. 1981). These neuroleptic-induced mouthing movements in rats may represent a behavioral correlate of human tardive dyskinesia. Waddington et al. (1981) have suggested that only chronic administration of neuroleptic drugs to rodents produces such perioral behaviour, and that the movements persist or are exacerbated after several weeks of drug withdrawal.

To examine neuroleptic-induced mouth movements in rats as a model of tardive dyskinesia, we have studied the perioral movements induced by 4 months' continuous administration of a range of neuroleptic drugs, and the effects of cholinergic manipulation on such movements induced by haloperidol. We find that chronic neuroleptic-induced orofacial movements in rats respond to cholinergic manipulation in the opposite way to human tardive dyskinesia.

Materials and Methods

Chronic Neuroleptic Drug Administration. Male Wistar rats (Bantin & Kingman; 205 ± 14 g at the start of the experiment) were initially housed in groups of eight and received approximately equivalent therapeutic doses of either haloperidol (2 mg/kg/day) trifluoperazine dihydrochloride (5 mg/kg/day), sulpiride (100 mg/kg/day) or clozapine (30 mg/kg/day). Drug doses were chosen from average daily clinical doses used in the control of schizophrenia (see Titeler and Seeman 1980), but increased five times to offset the greater drug metabolising ability of the rat. Haloperidol (Janssen Pharmaceutica) was dissolved in a minimum quantity of glacial acetic acid; sulpiride (SESIF, France) was dissolved in a minimum quantity of 2% sulphuric acid (v/v); and clozapine (Sandoz) was dissolved in a minimum quantity of 2 N hydrochloric acid. The resulting solutions were diluted to volume using distilled water. In each case the pH of the solution was adjusted to between 6.0 and 7.0 using 2 N sodium hydroxide. Trifluoperazine dihydrochloride (Smith, Kline & French) was dissolved in distilled water and stabilised with an amount of ascorbic acid equivalent to 10% of drug weight. Drugs were freely administered to rats via daily drinking water for a continuous period of 4 months. Age-matched

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control rats received distilled drinking water only. All animals were housed and observed under identical conditions of temperature (21 ± 3° C) and lighting (12 h light/dark cycle).

Cholinergic Manipulation of Neuroleptic-Induced Mouthing Behaviour. Cholinergic drugs and anticholinergic agents were all dissolved in distilled water and administered to naive rats prior to behavioral observation following 16–17 weeks of continuous neuroleptic administration. Animals were observed during the day between 8.00 and 18.00 hours. The effect of cholinergic activation on perioral behaviour was assessed in animals which received the acetylcholinesterase inhibitor physostigmine salicylate (0.2 mg/kg IP; 20 min previously) or the muscarinic agonist pilocarpine hydrochloride (4 mg/kg IP; 20 min previously). Decreased cholinergic function was achieved by administration of scopolamine hydrobromide (0.5 mg/kg IP; 50 min previously) or atropine sulphate (25 mg/kg IP; 20 min previously). The effects of peripheral cholinergic and anticholinergic manipulation induced by agents penetrating poorly into the brain were assessed using neostigmine bromide (0.2 mg/kg IP; 20 min previously) or scopolamine methylbromide (0.5 mg/kg IP; 50 min previously) respectively. All drugs were obtained from Sigma Chemical Co. Doses and timings chosen for observation of peak drug effects on mouthing behaviour were based on the activities of these compounds on yawning, a behavioural response believed to be under central cholinergic control (see Yamada and Furukawa 1980).

Assessment of Perioral Behaviour. Individual rats were observed on a clean table area measuring 45 × 15 cm. Following a 2-min acclimatisation period, the incidence of the following oral movements during a 5-min test period was recorded: tongue protrusion, wide mouth opening ("gaping") and "chewing" jaw movements. Where chewing behaviour was continuous, the number of individual jaw movements was recorded. The presence of teeth grinding or chattering in individual rats was also noted. All oral responses described were recorded only if they appeared to be purposeless, that is, if they did not occur in the context of goal-directed activity, such as licking or biting of objects, or grooming. The same animals were observed before and after administration of test drugs.

Statistical Analysis. Overall group differences between control and neuroleptic-treated animals were determined by use of the Kruskal-Wallis analysis of variance of ranks. Statistical analysis was then carried out using pair-wise Mann Whitney *U*-tests for data where Kruskal-Wallis *H* scores were associated with a probability of less than 5%. Mouthing responses were expressed as the mean values ± 1 SEM for a minimum of eight rats per drug treatment.

Results

At the time of behavioural testing, animals were still receiving continuous neuroleptic drug intake and had approximately doubled in weight. There was no difference in body weight in neuroleptic-treated rats compared to control animals (control, 404 ± 11 g; haloperidol 398 ± 8 g; trifluoperazine, 392 ± 6 g; sulpiride 400 ± 12 g; and clozapine 412 ± 8 g; $P > 0.05$.

The following daily drug intakes were achieved over the 4-month period: haloperidol, 1.4–1.6 mg/kg; trifluoperazine, 4.5–5.1 mg/kg; sulpiride, 102–110 mg/kg; and clozapine 23–26 mg/kg.

Table 1. Spontaneous oral behaviour in rats treated for 4 months with haloperidol, trifluoperazine, sulpiride or clozapine compared to age-matched control animals

Group	Incidence of movements/5 min			
	Chewing	Tongue protrusion	Gaping	Grinding teeth chattering (incidence in % of population)
Control	18.0 ± 2.7	1.5 ± 0.5	0	0
Haloperidol	44.7 ± 5.0*	2.4 ± 1.0	0	0
Trifluoperazine	32.2 ± 5.0*	4.0 ± 1.5	0	0
Sulpiride	30.6 ± 2.6*	1.7 ± 0.9	0	0
Clozapine	25.6 ± 4.9	3.0 ± 0.8	0	0

Values are mean ± 1 SEM for observations during a 5-min test period. $N = 8$. Rats received either haloperidol (1.4–1.6 mg/kg/day), trifluoperazine (4.5–5.1 mg/kg/day), sulpiride (102–110 mg/kg/day) or clozapine (23–26 mg/kg/day) for 4 months. Control rats received distilled drinking water only.

Overall group differences were determined using the Kruskal-Wallis analysis of variance of ranks. The following *H* scores and associated probabilities were obtained: chewing: $H = 15.798$, $P < 0.01$; tongue protrusion: $H = 2.184$, $P > 0.10$; gaping: $H = 0$, $P > 0.10$; teeth grinding: $H = 0$, $P > 0.10$. For data where $P < 0.05$, groups were compared by pairwise Mann Whitney *U*-tests

* $P < 0.05$ vs control, Mann Whitney *U*-test

Perioral Behaviour Induced by Chronic Neuroleptic Treatment. Perioral behaviour in control animals consisted of purposeless chewing jaw movements with occasional tongue protrusion (Table 1). Teeth chattering and wide mouth opening (gaping) usually did not occur. Animals treated chronically with haloperidol (1.4–1.6 mg/kg/day), trifluoperazine (4.5–5.1 mg/kg/day) or sulpiride (102–110 mg/kg/day) exhibited a higher frequency of chewing jaw movements with identical characteristics to those seen in control animals (Table 1). The frequency of tongue protrusion, gaping and teeth chattering, however, did not differ consistently from that observed in control rats (Table 1). In contrast, animals treated chronically with clozapine (23–26 mg/kg/day) did not exhibit a higher incidence of purposeless chewing or other oral behaviour than that observed in control animals (Table 1). Animals treated chronically with haloperidol showed the highest frequency of perioral movements and, therefore, were used in all subsequent experiments.

Effect of Cholinergic Manipulation of Perioral Behaviour: Cholinergic Agonists. Administration of the muscarinic agonist pilocarpine (4 mg/kg IP; 20 min previously) or the acetylcholinesterase inhibitor physostigmine (0.2 mg/kg IP; 20 min previously) increased the frequency of chewing jaw movements in control animals (Fig. 1). Tongue protrusion was increased by pilocarpine administration but not by physostigmine (Fig. 1). Administration of cholinergic agonists also induced more extreme jaw movements such as wide mouth opening (gaping), which were not observed either in control or in neuroleptic-treated animals (Fig. 1). Gaping

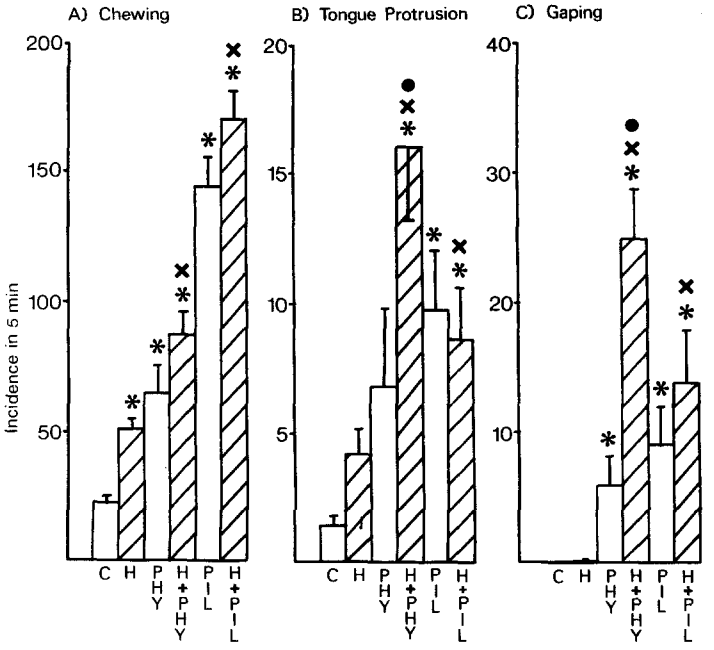

Fig. 1. Effect of pilocarpine (4 mg/kg IP) or physostigmine (0.2 mg/kg IP) on spontaneous perioral behaviour: (**A**) chewing, (**B**) tongue protrusion, or (**C**) gaping in rats treated chronically with haloperidol, compared to age-matched control rats. Values are mean ± 1 SEM for observations during a 5-min test period. $N = 10-24$. Rats received either haloperidol (*H*) (1.4–1.6 mg/kg/day) (hatched bars) for 4 months or distilled drinking water only (*C*) (open bars). Animals were observed before and 20 min after IP administration of either pilocarpine (*PIL*) (4 mg/kg) or physostigmine (*PHY*) (0.2 mg/kg). Overall group differences were determined using the Kruskal-Wallis analysis of variance of ranks. The following *H* scores and associated probabilities were obtained: chewing: $H = 65.818$, $P < 0.001$; tongue protrusion: $H = 35.063$, $P < 0.001$; gaping: $H = 51.419$, $P < 0.001$. For data where $P < 0.05$, groups were compared by pair-wise Mann Whitney *U*-tests. * $P < 0.05$, compared to control rats. × $P < 0.05$, animals treated with haloperidol plus a cholinergic agonist compared to haloperidol alone. ● $P < 0.05$, animals treated with haloperidol plus a cholinergic agonist compared to cholinergic agonist alone

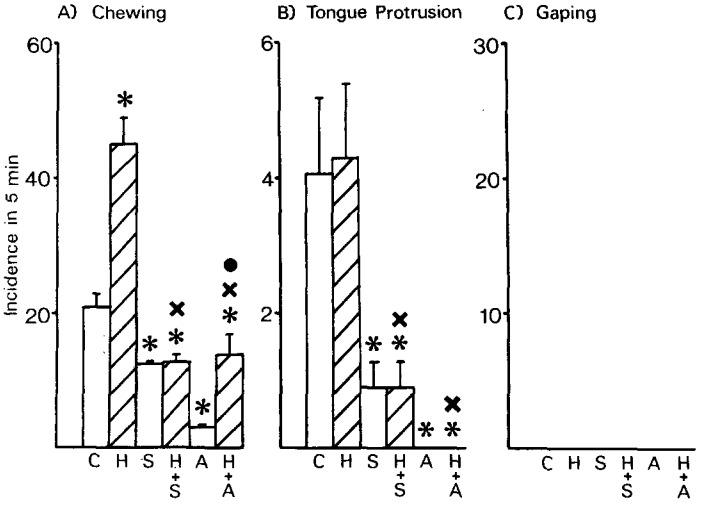

Fig. 2. Effect of scopolamine (0.5 mg/kg IP) or atropine (25 mg/kg IP) on spontaneous perioral behaviour: (**A**) chewing, (**B**) tongue protrusion, or (**C**) gaping in rats treated chronically with haloperidol, compared to age-matched control rats. Values are mean ± 1 SEM for observations during a 5-min test period. $N = 8-16$. Rats received either haloperidol (*H*) (hatched bars) (1.4–1.6 mg/kg/day) for 4 months or distilled drinking water only (*C*) (open bars). Animals were observed before and 50 min after IP administration of scopolamine (*S*) (0.5 mg/kg) or 20 min after atropine (*A*) (25 mg/kg IP). Overall group differences were determined using the Kruskal-Wallis analysis of variance of ranks. The following *H* scores and associated probabilities were obtained: chewing: $H = 45.324$, $P < 0.001$; tongue protrusion: $H = 18.365$, $P < 0.01$; gaping: $H = 0$, $P > 0.10$. For data where $P < 0.05$, groups were compared by pair-wise Mann Whitney *U*-tests. * $P < 0.05$, compared to control animals. × $P < 0.05$, animals treated with haloperidol plus a cholinergic antagonist compared to haloperidol alone. ● $P < 0.05$, animals treated with haloperidol plus a cholinergic antagonist compared to cholinergic antagonist alone

normally was preceded by periods of continuous chewing jaw movements. Gaping usually occurred in bursts of three or four mouth openings, and was followed by repeated tongue protrusion and chewing. The incidence of teeth chattering was not increased by administration of either pilocarpine or physostigmine to control rats.

In animals treated chronically with haloperidol (1.4–1.6 mg/kg/day), administration of either pilocarpine (4 mg/kg IP; 20 min) or physostigmine (0.2 mg/kg IP; 20 min) increased the frequency of purposeless chewing jaw movements to a similar extent to their effects in control rats (Fig. 1). Pilocarpine increased tongue protrusion in haloperidol-treated rats to a similar extent to that produced by administration of pilocarpine to control rats. Physostigmine-induced tongue protrusion was increased to a greater extent in haloperidol-treated rats than in control rats treated with physostigmine alone (Fig. 1). As in control animals, cholinergic agonists again induced abnormal gaping behaviour which was not observed spontaneously in haloperidol-treated animals (Fig. 1). However, haloperidol-treated rats when challenged with physostigmine (0.2 mg/kg IP) exhibited an incidence of gaping jaw movements greater than that observed in control animals receiving physostigmine alone. This effect was not observed following acute pilocarpine administration (Fig. 1).

Anticholinergic Drugs. Administration of the anticholinergic agents scopolamine (0.5 mg/kg IP; 50 min previously) or atropine (25 mg/kg IP; 20 min previously) reduced spontaneous chewing in control rats and tongue protrusion was virtually abolished (Fig. 2). Gaping mouth opening was observed neither in the absence nor following anticholinergic treatment in control rats (Fig. 2). In animals treated with haloperidol for 4 months, acute administration of anticholinergic agents reduced chewing movements to or below values for control animals (Fig. 2) and, again, virtually abolished tongue protrusion (Fig. 2). Gaping was not induced by anticholinergic administration to haloperidol-treated rats (Fig. 2).

Peripheral Cholinergic Manipulation. The cholinergic agonist neostigmine (a peripheral acetylcholinesterase inhibitor) (0.2 mg/kg IP; 20 min previously) did not alter spontaneous chewing or tongue protrusion in control animals, and did not

Table 2. Effect of peripheral cholinergic manipulation on spontaneous perioral behaviour (chewing, tongue protrusion or gaping) in rats treated chronically with haloperidol compared to age-matched control rats

Group	Incidence of movement/5 min		
	Chewing	Tongue protrusion	Gaping
A. Neostigmine (0.2 mg/kg IP)			
Control	15.1 ± 4.3	1.5 ± 0.8	0
Haloperidol	39.6 ± 6.0*	0.9 ± 0.4	0
Neostigmine	20.9 ± 8.3	0.6 ± 0.5	0
Neostigmine plus haloperidol	28.4 ± 5.1*	0.4 ± 0.2	0
B. Methyl scopolamine (0.5 mg/kg IP)			
Control	15.9 ± 2.7	1.3 ± 0.5	0
Haloperidol	45.4 ± 12.0*	3.9 ± 0.8	0
Methyl scopolamine	19.2 ± 4.6	1.5 ± 0.7	0
Methyl scopolamine plus haloperidol	46.5 ± 14.3*•	2.5 ± 1.1	0

Overall group differences were determined using the Kruskal-Wallis analysis of variance of ranks. The following H scores and associated probabilities were obtained.

A Neostigmine: chewing: $H = 7.812$, $P < 0.05$; tongue protrusion: $H = 1.467$, $P > 0.10$; gaping: $H = 0$, $P > 0.10$.

B Methyl scopolamine: chewing: $H = 13.867$, $P < 0.01$; tongue protrusion: $H = 6.756$, $P > 0.05$; gaping: $H = 0$, $P > 0.01$.

Values are means ± 1 SEM for observations during a 5-min test period. $N = 8$. Rats received either haloperidol (1.4–1.6 mg/kg/day) for 4 months, or distilled drinking water only. Animals were observed before and after administration of neostigmine (0.2 mg/kg IP, 20 min previously) or methyl scopolamine (0.5 mg/kg IP, 50 min previously). For data where $P < 0.05$, groups were compared by pair-wise Mann Whitney U-tests. * $P < 0.05$ vs control, Mann Whitney U-test, • $P < 0.05$ animals treated with haloperidol plus a peripheral cholinergic agent, compared to peripheral cholinergic agent alone

induce gaping (Table 2A). Neostigmine did, however, occasionally induce uncoordinated, rapid twitching of superficial muscles in the cheeks which were not associated with movements of the mouth. In animals treated chronically with haloperidol (1.4–1.6 mg/kg/day) for 4 months, neostigmine did not affect chewing, tongue protrusion or gaping (Table 2A). Administration of the peripherally-acting anticholinergic agent methyl scopolamine (0.5 mg/kg IP; 50 min previously) did not reduce chewing or tongue protrusion in control rats (Table 2B). In haloperidol-treated rats, chewing or tongue protrusion were not reduced by methyl scopolamine (Table 2B). Gaping was not observed in any animal (Table 2B).

Discussion

Administration of haloperidol, trifluoperazine or sulpiride, but not clozapine, to rats for 4 months increased the frequency of purposeless chewing jaw movements usually without affecting other perioral responses (tongue protrusion, mouth opening and teeth chattering). These findings are in general agreement with other studies involving administration of a variety of neuroleptic drugs (Sahakian et al. 1976; Clow et al. 1979; Howells and Iversen 1979; Waddington and Gamble 1980; Waddington et al. 1981). Enhancement of chewing behaviour in the present study was first recorded following 4 weeks' neuroleptic treatment, and was maintained at a similar level throughout the subsequent administration of neuroleptic drugs for 9 months. This persistence of perioral behaviour contrasts with the development of tolerance to neuroleptic-induced catalepsy after 3 months' drug treatment, and the return of locomotor activity to normal levels after 6 months' treatment or less (unpublished observations; Sahakian et al. 1976). In the present study we did not observe any increase in the frequency of teeth chattering in neuroleptic-treated rats. In contrast, Iversen and colleagues (1980) found fluphenazine to enhance this component of perioral behaviour. The induction of teeth chattering may depend on the particular neuroleptic drug employed. Thus, Bourne and colleagues (1982) showed an enhancement in rats treated for 6 months with metoclopramide or piflutixol, but not in haloperidol-treated animals.

Purposeless chewing in rats has usually been observed after some months of neuroleptic intake. At this time functional striatal dopamine receptor supersensitivity exists, as judged by enhanced apomorphine-induced stereotypy and an increase in ^{3}H-spiperone binding. It is this change in man which is thought responsible for the onset of tardive dyskinesias. It could be considered that the perioral movements in the rat, induced by neuroleptic drugs, represent a manifestation of tardive dyskinesia, but there are reasons for dismissing this idea. Tardive dyskinesia in man is reduced in intensity by drugs increasing cholinergic function and exacerbated by anticholinergic agents (see Kazamatsuri et al. 1972; Baldessarini and Tarsy 1978; MacKay and Sheppard 1979; Jenner and Marsden 1982). However, this study has demonstrated that the perioral movements in rats are altered in the opposite direction by drugs manipulating cholinergic function. Thus, in both normal and neuroleptic-treated animals, cholinergic agents increased mouthing movements while anticholinergic drugs caused a decrease. (Both cholinergic and anticholinergic drugs induce peripheral side effects, such as hypersalivation or dryness of the mouth, that might cause an apparent change in perioral movements. Whilst we have not examined whether the effects of cholinergic agonists could be blocked by peripheral blockade with methyl scopolamine, the peripherally-acting cholinergic drugs we employed had no effect on mouthing movements in either control or neuroleptic-treated animals. This suggests that cholinergic manipulation of these movements is central in origin.)

The time course of induction of perioral movements also does not mimic that of tardive dyskinesias in man. While Waddington and colleagues (1981) maintain that chronic neuroleptic treatment is required for the induction of perioral behaviour, others have observed chewing following a few days or weeks of neuroleptic intake (Sahakian et al. 1976; Howells and Iversen 1979; unpublished observations). Finally tardive dyskinesias in man persist or are exacerbated on withdrawal of neuroleptic therapy. However, while Waddington and colleagues (1981) have claimed persistence of perioral movements in rats, we have been unable to confirm this in any of our long-term neuroleptic studies involving a variety of neuroleptic drugs.

What do these perioral movements in rats represent in terms of extrapyramidal disturbances caused by neuroleptic drugs in man? Acute dystonic reactions in man (see Marsden and Jenner 1980), and in primates (Meldrum et al. 1977; Casey et al. 1980; Porsolt and Jalfre 1981), are enhanced by cholinergic agents and alleviated by anticholinergic drugs.

The cholinergic manipulation of the perioral movements induced in rats by neuroleptic treatment might suggest a resemblance to acute dystonia. Indeed, excessive chewing and tongue protrusion in rats may occur following administration of cholinergic agonists after only a single dose of fluphenazine enanthate (Yamada and Furukawa 1980). It was of interest that chronic administration of clozapine, an atypical neuroleptic, did not induce abnormal mouthing behaviour in rats. This may be due to the high inherent anticholinergic activity of this drug (Stille et al. 1971; Miller and Hiley 1974). Clinically the use of clozapine has not been associated with the induction of acute dystonia in man, and, unlike classical neuroleptics, clozapine does not induce acute dystonic reactions in primates (Porsolt and Jalfre 1981).

In conclusion, despite the chronic nature of neuroleptic-induced perioral behaviour in rats, our findings indicate that they do not represent an animal correlate of tardive dyskinesia. Whilst the effects of central cholinergic manipulation suggest that these movements more closely resemble acute dystonic reactions, there are reasons for not equating the conditions.

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