Scand. J. Lab. Anim. Sci. No. 4. 1999. Vol. 26

# Chronic intermittent treatment with Clozapine: implications for development of vacuous chewing movements and electrical kindling

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*Introduction*

Long-term treatment of patients with classical antipsychotic drugs can lead to development of tardive dyskinesia, a syndrome characterized by repetitive involuntary movements of the mouth and tongue. Also administration of anti-dopaminergic drugs to rats results in increased oral activities scored as vacuous chewing movements (VCM) and tongue protrusions (*Clow et al., 1979; Rupniak et al., 1985; Gunne et al., 1986; Glenthoj and Hemmingsen, 1989; Waddington, 1990; Glenthoj et al., 1990; Peacock et al., 1990; Glenthoj, 1993*). This syndrome appears to show several characteristics of tardive dyskinesia. It is evident in a proportion of animals only (*Waddington et al., 1985*), it is more often seen in older than in younger animals (*Waddington et al., 1985; Waddington et al., 1986*), and in some studies the perioral movements either emerge or persist for a shorter or longer period after discontinuation of antipsychotic treatment (*Waddington et al., 1983; Waddington et al., 1985; Waddington et al., 1986; Ellison et al., 1987; Glenthoj and Hemmingsen, 1989; Glenthoj et al., 1990; Glenthoj, 1993*). According to Casey (*Casey, 1987*) increases in spontaneous oral activity might qualify as an analogous animal model of tardive dyskinesia. Evaluating spontaneous perioral movements in rodents during chronic antipsychotic treatment a marked inconsistency is found. Obvious reasons for differences are the use of different rat strains (*Tamminga et al., 1990*) differences in testing procedures (*Levy et al., 1987; Waddington, 1990; Glenthoj et al., 1990*), differences in the animals environment (*Glenthoj and Hemmingsen, 1991*) and differences in treatment regimen (*Glenthoj and Hemmingsen, 1989; Glenthoj et al., 1990; See and Ellison, 1990b*).

Development of persisting increases in oral activity in animals treated intermittently with classical antipsychotic drugs, but not with a selective dopamine $D_1$ antagonist, has been demonstrated (*Glenthoj et al., 1990; Glenthoj, 1993; Glenthoj et al., 1993; Glenthoj, 1995*). Increases in VCM following continuous treatment disappeared after withdrawal. The observed sensitization of dyskinetic side effects following discontinuous treatment was proposed to represent an animal model of tardive dyskinesia. Furthermore, intermittent as opposed to continuos treatment with a dopamine $D_2$ receptor antagonist (haloperidol) facilitated seizure development in electrical amygdala kindling (*Glenthoj et al., 1993a*).

Based on the observed cross-sensitivity between persisting increases in oral activity following withdrawal from discontinuous treatment with haloperidol and electrical kindling, common mechanisms in development of tardive dyskinesia and electrical amygdala kindling have been suggested (*Glenthoj et al., 1993a; Glenthoj, 1995*). An objection to this hypothesis, however, is that the observed cross-sensitivity might instead be the result of intermittent treatment with a drug known to lower seizure threshold.

Clozapine is more inclined to lower seizure threshold than most classical antipsychotics, but it does not cause development of dyskinesia in humans (*Tamminga et al., 1994*). Opposed to classical antipsychotic drugs, clozapine occupies less than 60% of the brain dopamine $D_2$ receptors in clinically relevant doses _ (*Farde and Nordstrom, 1992*). However, clozapine binds to other subtypes of dopamine receptors including dopamine $D_1$-, $D_3$-, $D_4$-, and $D_5$- receptors and to serotonin, 5-$HT_{1A}$-, $5HT_{1c}$-, $5HT_2$-, and $5HT_3$-receptors, as well as $\alpha_1$, $\alpha_2$, muscarinic, and histaminergic receptors (*Snyder et al., 1974; Coward et al., 1989; Sokoloff et al., 1990; Van Tol et al., 1991; Coward, 1992*).

The aim of this study was to examine the relation between development of dyskinetic mouth movements and increased disposition to seizure development following electrical kindling in clozapine treated rats. We tested the occurrence of persisting increases in oral movements in rats treated discontinuously with two different doses of clozapine for 16 weeks and the subsequent development of generalized seizures following electrical amygdala kindling in the same animals. This was done in order to examine whether long-lasting, intermittent treatment with clozapine would result in dyskinetic mouth movements as has been demonstrated following treatment with haloperidol. Furthermore, we wanted to test the previously suggested hypothesis of a connection between dopaminergic sensitization, measured as persistent increases in oral activity, and seizure development.

## *Materials and Methods*

### *Subjects*

Experiments were carried out using 45 male Wistar rats (Møllegård, Denmark) aged 2.5 month at the beginning of the study. The rats were randomly divided into 3 groups: Group 1: 15 control rats receiving placebo. Group 2: 15 rats treated with clozapine 15 mg/kg (b.i.d.). Group 3: 15 rats treated with clozapine 30 mg/kg (b.i.d.). Rats were kept individually in clear plexiglass cages in a room with 12-hour light-dark cycle (light on 8 a.m.-8 p.m.). They had free access to standard laboratory diet and water. The weight of the rats was registered every second week. During the medication period of the study, 2 rats in group 3 died. Two weeks after termination of medication, 32 rats were randomly allocated (11 rats from each of the groups 1 and 2, and 10 rats from group 3) for electrode implantation as described below. During kindling 1 rat in group 2 died. One rat was lost prior to histological examination, 2 animals were excluded, as electrode placement could not be verified, 1 animal was excluded due to electrode placement outside the nucleus amygdala.

### *Drug administration*

Clozapine, dry matter (Sandoz), was dissolved in a small volume of HCl and after dilution with distilled water the pH was adjusted to 5.0-5.5 with NaOH. The drug was administered twice daily (morning and late afternoon) for two consecutive days by a gastric tube in doses of 15 or 30 mg/kg followed by five drug free days. The treatment period was 16 weeks. The control group received a corresponding volume of 0.1 M acetic acid adjusted to pH 5.0-5.5 with NaOH. The clozapine doses were chosen based on preceding experiments demonstrating that during an 48 hr treatment period 24 rats receiving 15 mg/kg (b.i.d.), and 24 rats receiving 30 mg/kg (b.i.d.), obtained serum clozapine levels within the range used in human treatment (*Bille and Olesen, unpublished data*). In a cross-sectional study of 30 schizophrenic patients in steady state treatment the median serum clozapine concentration, measured 12 hours after last drug intake, was 1076 nmol/l and ranged from 196 to 5581 nmol/l (*Olesen et al., 1995*).

Clozapine in serum was determined by an on-line HPLC method previously described (*Olesen and Poulsen, 1993*).

### *Vacuous chewing movements*

Before the study all animals were habituated to plexiglass tubes 6 times for 15 min. Habituation sessions were repeated between observation weeks (3 times during the week before observation). The animal's head protruded through a hole in one end of the tube. The size of the tubes was changed with the growth of the animals during the study. Both the size of the tubes and the size of the head holes were adjusted to the size of the individual rat in such a way that the animal was fixed without being squeezed.

Behavioural observations were made between 9 a.m. and 2 p.m. the day before treatment and the first drug free day after treatment in treatment weeks 1, 7, and 16. Following drug withdrawal observations were made after 1, 2, and 3 weeks.

For home cage observations, the animals in their home cages (clear plexiglass cages) were placed on a table in a quit room 1 h before observations. At each observation rats were observed for vacuous chewing movements; non-object directed chewing movements, three times for 2 minutes. The total numbers of vacuous chewing movements were recorded. One observer (AB) who was blind to the treatment schedule scored home cage behaviour.

After observation in home cages, the rats were rehabituated to a plexiglass tube for 6 min before they were videotaped for 6 min. The animals were rehabituated to the tubes in order to minimize the stress artefact of the tubes and make observations more easy and reliable (see *Glenthøj, 1995*). The videocamera was aimed towards the right side of the rat's head at approximately 45( from the floor. The videotapes were rated blindly at the end of the study by one observer (AB) who was unaware of the treatment given and the treatment day. The total numbers of vacuous chewing movements were recorded. Often it was necessary to observe the animals in slow motion to obtain the correct number.

*Surgery*

Twenty-one days after drug withdrawal the rats were anaesthetised with equithesine i.p. and mounted in a stereotaxic apparatus. Bipolar stainless steel electrodes were implanted into the left nucleus amygdala (2.8 mm posterior to bregma, 5 mm lateral to midline and 7.8 mm below dura). The electrodes were implanted through drilled holes and attached to the skull by stainless steel screws. The electrodes and screws were held in place with dental acrylic cement.

*Electrical kindling procedure*

Two weeks after electrode implantation, kindling was induced by means of daily stimulation's in the left nucleus amygdala (2 s trains of 1 ms pulses at 60 Hz). The stimulation current for each rat was set at 10% above the threshold current for inducing after-discharge. The animals were stimulated daily until fully kindled seizures were induced, though maximally 39 days. Seizures were rated using the severity scale of Racine (*Racine, 1972*) modified to include falling on the back without prior rearing as grade 5. Thus, the seizures were rated as follows. Grades: (1) facial clonus; (2) as grade 1 with neck clonus; (3) as grade 2 with forelimb clonus; (4) as grade 3 with trunk clonus and rearing; (5) as grade 4 with hindlimb and tail clonus and falling.

*Histology*

After electrical kindling the rats were killed in deep halothane anaesthesia by transcardiac infusion of 10% formalin in phosphate-buffered saline (pH =7.4). The brains were removed and post fixed in the same fixative, dehydrated in increasing concentrations of alcohol, and subsequently embed in paraffin. Frontal sections (2-3 µm) comprising the nucleus amygdala, were cut on a microtome, and stained according to the Klüver-Barrera method. Microscopic evaluation was performed for all animals, and included electrode placement and nucleus amygdala neuropathology. Electrode placement was considered correct if the electrode track showed that the electrode tip had been placed inside or at the border of the nucleus amygdala.

*Statistical analysis*

The statistical analyses have been carried out using non-parametric techniques. In case of variables, which attain a limited number of values and where distributional properties are unknown; Wilcoxon signed rank tests (within group comparisons) and Mann Whitney (Kruskal Wallis) tests have been applied. The analysis of categorical variables ordinary Chi-square tests (or exacts tests when sparse tables) have been applied. The analyses of

kindling stimulus data have been conducted by means of logistic regressions with the frequency of seizures (at fixed grades) as dependent variables and time as independent variable.
All statistical tests have been two-sided and the levels of statistical significance have all over been 5%.

*Results*

*Animal weight.*
A statistical significant difference in weight gain was found. (fig 1). The group receiving 30 mg/kg (b.i.d) had a substantial lower weight gain than the placebo treated group.

*Vacuous chewing movements.*
The mean number of episodes of vacuous chewing movements observed in home-cages and tubes on the day before treatment in week 1, the day immediately after treatment in week 1, week 7, and week 16, and 3 weeks after drug withdrawal are shown in fig 2 and fig 3.
The group treated with clozapine 30 mg/kg had higher mean values in week 1, week 7, and week 16, compared to the other groups, due to a larger variation in this group. No statistical between-group differences were recognized. Furthermore, no statistically significant within-group differences were found.

*Fig 1*: From two weeks of treatment the clozapine treated groups had a lower weight than the placebo group. (CI: 95%).

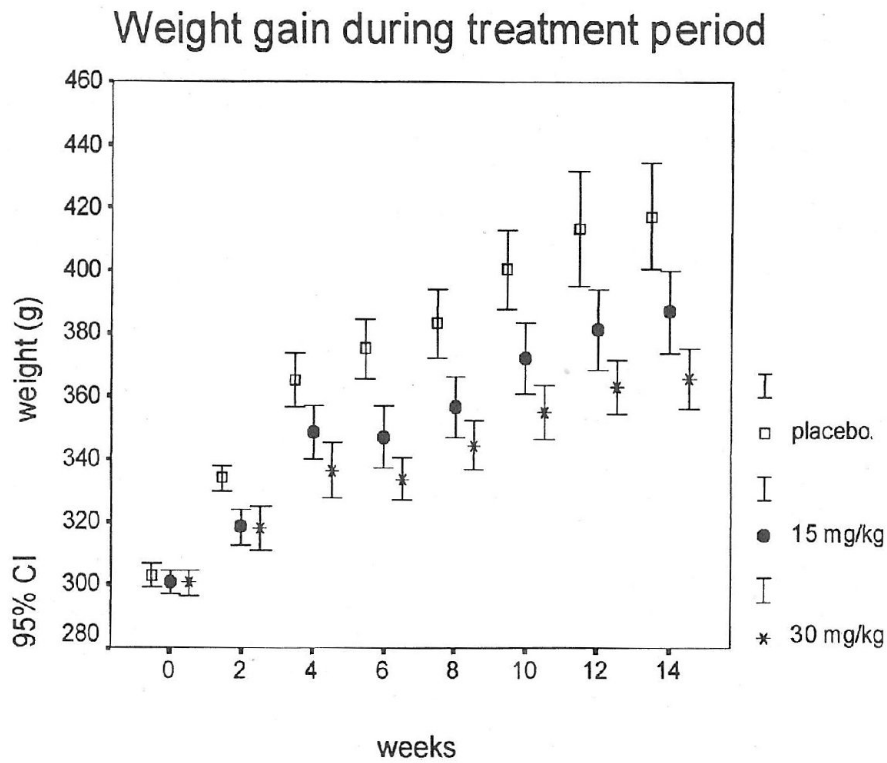


*Fig 2*: Distribution of VCM (Box-plot: 10%, 50%, 90%). Across three groups five timepoints. Animals were observed for three times 2 min in home-cages at following timepoints: the day before first treatment, the day immediately after treatment in week 1, 7, 16, and 3 weeks (week 19) after withdrawal from clozapine.

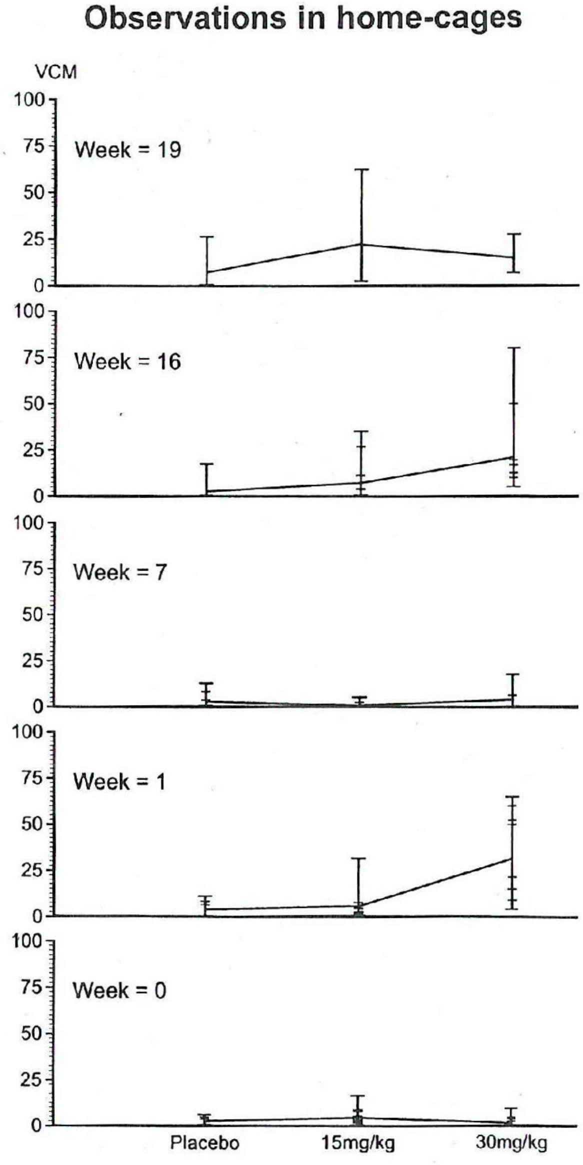
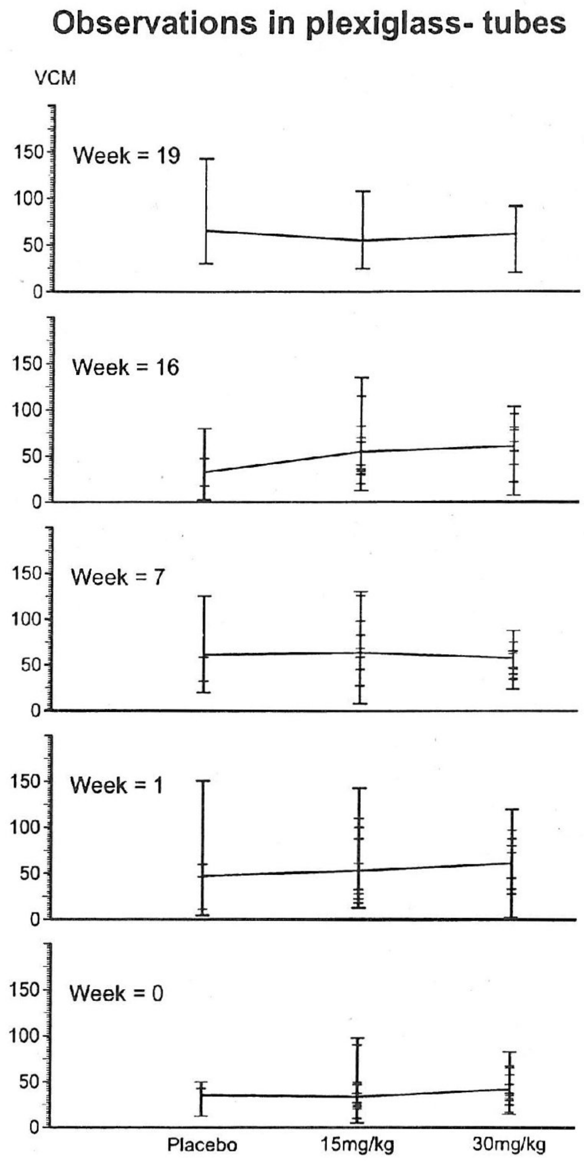


*Fig 3*: Distribution of VCM (Box-plot: 10%, 50%, 90%). Across three groups five timepoints. Animals were observed for 6 min in plexi-glass tubes at videotape obtained at following timepoints: the day before first treatment, the day immediately after treatment in week 1, 7, 16, and 3 weeks (week 19) after withdrawal from clozapine.



*Electrical kindling*

Tests of fit (F-tests) of the logistic regression curves predicting the probability of seizure (grade x, $x \geq 1, 2, 3, 4$ and 5) for a given stimulation confirmed the validity of the regression curves for all groups of animals and for all values of grade x ($P \leq 0.05$). Inspection of the estimated slope values (marginal effect of change of stimulation on probability of having seizure) showed no group differences. (fig 4).

*Histology*

Two animals were . excluded, as electrode placement could not be verified, 1 animal was excluded due to electrode placement outside the nucleus amygdala. In 3 animals calcification was found around the electrode tracks, and in 2 animals sparse haemorrhage was found.

*Discussion*

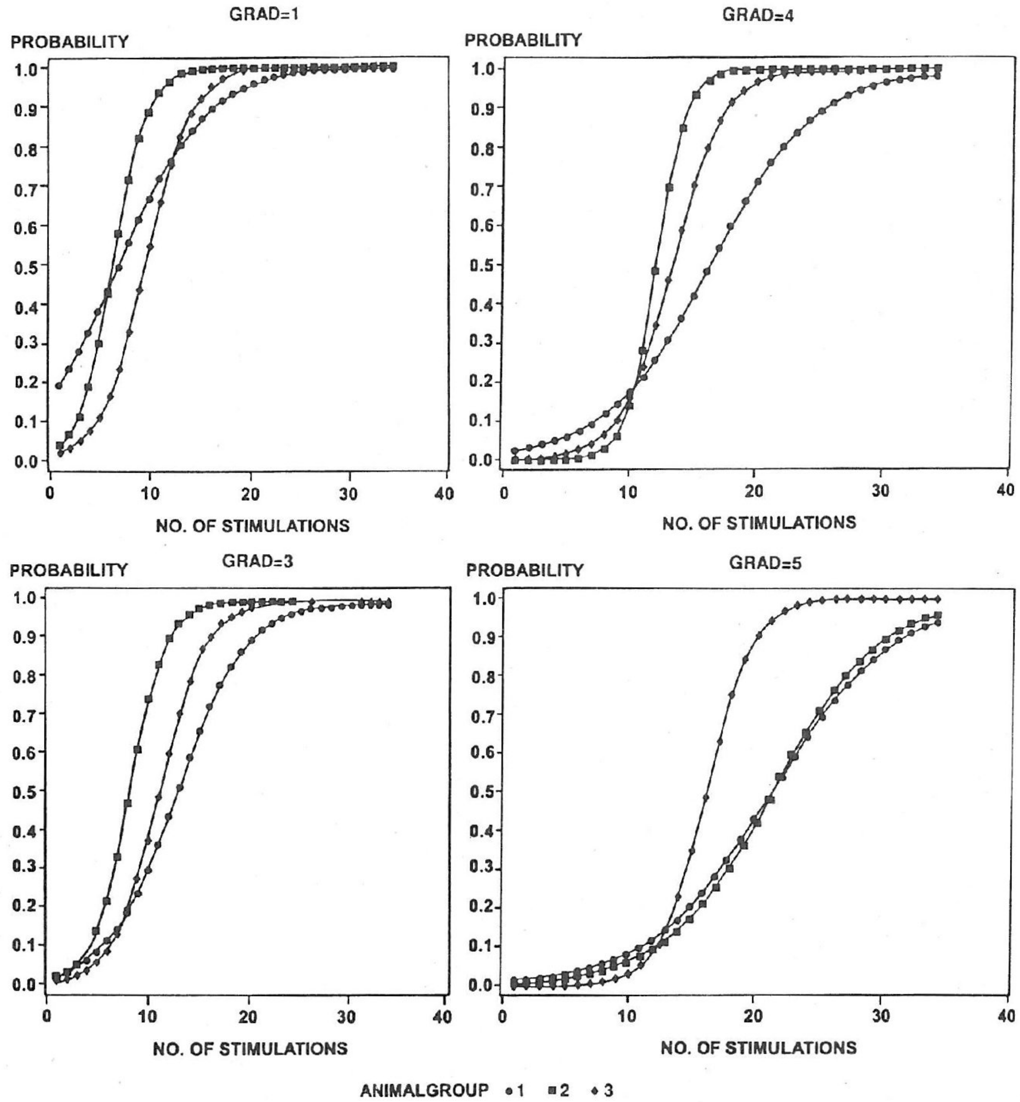
The main findings of the study was that long lasting intermittent treatment with clozapine, neither resulted in persisting increases in oral activity measured as vacuous chewing movements, nor influenced the course of succeeding electrical amygdala kindling. The results are in contrast to what we have previously demonstrated with identical methods following treatment with haloperidol (*Glenthoj et al. 1993a);* However, the failure of clozapine to influence oral activity is in agreement with both an experimental study (*See and Ellison, 1990a*) and clinical experience.

Cross-sensitivity between development of dyskinetic mouth movements following intermittent treatment with a classical antipsychotic drug (haloperidol) and electrical amygdala kindling has previously been demonstrated (*Glenthoj and Hemmingsen, 1989; Glenthoj et al. 1993a*). Microinjections of GABA agonists in substantia nigra pars reticulata suppress, whereas injections of GABA antagonists enhance seizures (*Iadarola and Gale, 1982; Turski et al. 1986)*. This finding has implications for both conditions, and it was suggested that depressed gamma-amino butyric acid (GABA) activity in substantia nigra could be a common mechanism in the development of kindled seizures and sensitization of the motoric part of the dopaminergic system resulting in development of dyskinetic mouth movements (*Glenthoj, 1995*).

The finding that intermittent treatment with an antipsychotic drug that lower the seizure threshold without causing persisting dyskinetic mouth movements, does not enhance development of kindled seizures is predictable from the hypothesis of common pathogenetic mechanisms in kindling and dopaminergic sensitization. Moreover, clozapine, as opposed to haloperidol, is known to inhibit limbic system kindling when administered during the kindling procedure (*Graham and Kokkinidis, 1993).*This ability of the drug is probably related to its preferential limbic and prefrontal site of action (*Huff and Adams, 1980; Chen et al. 1991*) and to clozapins enhancing effects on the GABA-ergic system (*McPherson et al. 1987*). Clozapine increases GABA release in the ventral striatum while haloperidol increases GABA release in the globus pallidus (*Drew et al. 1990*). These regional differences in the effects on GABA release may parallel the unique profiles of these drugs, and may contribute to its atypical limbic site of action (*Kinon and Lieberman, 1996).* Furthermore, it might explain a tendency towards greater disappearance of tardive dyskinesia in patients treated with clozapine compared to a control group treated with classical antipsychotics (*Peacock et al. 1996*). A model for development of anti-dopaminergic induced sensitization of the nigro-striatal dopaminergic system including simultaneous potentiation of the GABA-ergic striato-substantia nigra pars reticulata pathway and breakdown of GABA-ergic function in substantia nigra has been suggested (*Glenthoj, 1995*). The specific action of clozapine in the limbic GABA-ergic system could explain why the drug does neither cause sensitization of the motoric part of the dopaminergic system nor potentiate seizure development in kindling.

In conclusion: The present study is in agreement with the supposition of vacuous chewing movements being a valid animal model for tardive dyskinesia as no persistent increases were found following long-lasting treatment with a drug that does not cause development of tardive dyskinesia in patients. Moreover, the result clearly refuted that accelerated kindling following discontinuous

*Fig 4*: Fitted response curves from logistic regression analysis. Four levels of seizure activity (grade=1,3,4,5) within each three animal group.



treatment with a typical antipsychotic drug is the result of treatment with a drug known to lower the seizure threshold. The present findings are consistent with the hypothesis of common pathogenetic mechanisms in the development of persisting increases in oral activity and in electrical amygdala kindling. The ability of clozapine to inhibit limbic system kindling point to this drug as superior to classical antipsychotic drugs in preventing spontaneous sensitization of the meso-limbic dopaminergic system, and hereby possibly aggravation of psychotic symptoms (*Haracz, 1982; Sato, 1983; Lieberman et al. 1990; Glenthoj et al. 1993b; Glenthoj, 1995; Glenthoj and Hemmingsen, 1997*). Whether the favourable profile according to motoric side-effects and therapeutic action is related to modulation of the dopaminergic system by simultaneous blockade of 5-$HT_2$ receptors, dopamine $D_1$ receptors or possibly other receptor systems is as yet unknown. Further studies of the new atypical antipsychotic drugs and with compounds selective for a broad spectrum of receptors are necessary in order to interpret the meaning of interactions between different transmitter systems for development of side-effects and clinical efficacy.

*Acknowledgements*

This study was supported by the Lundbeck Foundation, Glaxo A/S, the Schizophrenia Foundation of 1986, the Ivan Nielsen's Foundation, the Psychiatric Research Foundation of 1967, the Eli and Egon Larsen's Foundation, and the Funds to promote Psychiatric Basic Research. Clozapine was kindly provided by Sandoz Pharma AG, Basel/Schweiz. The authors thank Allan Hansen for assistance in implanting electrodes and for technical assistance and Peter Allerup for statistical assistance.

*Summary*

Intermittent treatment of rats with clozapine in two different doses for 16 weeks did neither result in sensitization of oral activity nor in facilitation of seizure development in electrical kindling. The lack of development of dyskinetic mouth movements concerts with clinical experience. Cross-sensitivity between development of dyskinetic mouth movements following long-lasting intermittent treatment of rats with haloperidol and electrical amygdala kindling has previously been demonstrated. The findings in this study contradict that cross-sensitivity between intermittent treatment with classical antipsychotic drugs and electrical amygdala kindling is the result of the lowering of seizure threshold of antipsychotic drugs. Instead the present results support the hypothesis of common pathogenetic mechanisms in the development of persisting increases in oral activity and in electrical amygdala kindling.

Keywords: Oral dyskinesia; Clozapine; Sensitization (pharmacological); Amygdala kindling.

*Summary*

Intermitterende behandling af rotter med med clozapine gav ikke anledning til hverken sensitivering af oral aktivitet eller øget krampetilbøjelighed ved elektrisk kindling. Den manglende udvikling af dyskinetiske mund-bevægelser er i overensstemmelse med kliniske erfaringer med clozapin.

Tidligere er påvist krydssensibilitet mellem udvikling af dyskinetiske mundbevægelser, efter langvarig intermitterende behandling af rotter med haloperidol, og elektrisk amygdala kindling.

Resultaterne fra dette studie afkræfter, at krydssensibilitet mellem intermitterende behand-ling med klassiske antipsykotika og elektrisk amygdala kindling er et resultat af at krampetærskelen er sænket. Derimod støtter resul-taterne hypotesen om fælles patogenetiske mekanismer ved udvikling af vedvarende øget oral aktivitet og elektrisk amygdala kindling.

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