Oral tardive dyskinesia in the rat

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Oral tardive dyskinesia may develop due to neuroleptic therapy as a drug-induced disorder of the dopaminergic system of the brain. Long-term treatment with a neuroleptic drug impairing dopaminergic neurotransmission in the rat brain augments oral dyskinetic responses to dopaminergic agonists like apomorphine. In the present experiments, rats were pretreated daily with haloperidol for 3 weeks to cause a 'chronic' blockade in the striatal dopamine receptors. After a withdrawal period of 3 and 6 days, oral sensory stimulation was applied. On the following day the same groups were given apomorphine, and the oral stimulation was repeated. The rats pretreated daily with haloperidol had significantly higher dyskinesia scores than the rats pretreated with saline. The main observation with these sensitized rats was an increase in the frequency and intensity of experimental bruxism caused by oral sensory stimulation alone. Sensory impulses are known to cause release of dopamine in the nigrostriatal system. The combination of oral sensory stimulation and central dopaminergic supersensitivity in the rat can be regarded as an animal model for oral symptoms in human dyskinesia.
☐ *Masticatory muscles; experimental bruxism; dopaminergic system; neuroleptic drugs*

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Human tardive dyskinesia (TD) is a hyperkinetic syndrome that is regarded as a drug-induced disorder of the dopaminergic systems of the brain (18). The syndrome is characterized by a variable mixture of orofacial dyskinesia, chorea, athetosis, and dystonia. It is principally localized in the oral region, where it is known as the buccolinguo-masticatory or BLM syndrome (9). Insidious in onset, it may begin as mild tongue movements, followed later by more obvious movements of the tongue and the lips, rhythmical chewing movements, jaw deviations, facial grimacing, and eye blinking (11).

TD symptoms may worsen with emotional stress or be alleviated by relaxation (18). TD can interfere with speech and produce oral ulcerations (11). It may also result in aversion to wearing dentures. Clinical experience suggests that occlusal imbalance is important as a factor triggering TD symptoms, e.g. bruxism (27).

TD is usually a delayed iatrogenic phenomenon of neuroleptic therapy in psychotic or nonpsychotic patients (13). It is not part of the schizophrenia, but is now recognized as a major adverse effect of chronic antipsychotic therapy (3). TD can occur at any time during treatment but is especially frequent when medication has been diminished or stopped. TD was defined by Faurbye et al (9). They differentiated it from a 'spontaneous' dyskinetic syndrome, occurring, for example, in psychotic mannerism.

Originally, Klawans (12) suggested that the mechanism of TD is 'chemical denervation hypersensitivity'. Neuroleptics block dopamine receptors of the striatum in the extrapyramidal system. After prolonged use of a neuroleptic drug, the receptors compensate for the block by a functional adjustment and become supersensitive to dopamine, and TD is thus the manifestation of the excessive activity of such receptors.

An animal model of tardive dyskinesia

Long-term treatment with a neuroleptic drug impairing dopaminergic neurotransmission in the rat brain has been found to augment oral behavioral responses to dopaminergic agonists like apomorphine (10, 24). In the early phase, the phenomenon is thought to be related to the blockade of inhibitory presynaptic receptors, and later,

to increase of the sensitivity of postsynaptic dopamine receptors (14). Functional supersensitivity of dopamine receptors can be revealed only by stimulation with dopamine or its agonist. However, stress appears to be synergistic with dopamine agonists and may account for the oral syndromes associated with dopaminergic dysfunction (10, 19).

An animal model for TD has been introduced. It applies the response to a dopamine agonist in rodents made behaviorally supersensitive by pretreatment with a neuroleptic drug (6, 17, 24). In this situation, the rat responds to apomorphine with enhanced and prolonged oral stereotypy (gnawing and biting). The functional sensitization to dopaminergic stimulation persists for several weeks after withdrawal of the neuroleptic drug (23).

In this study, oral function was impaired by limiting dental occlusion to the incisors. The aim was to elucidate the interaction between functionally supersensitive dopamine receptors and oral sensory stimulation by using the animal model for TD.

Material and methods

Male Wistar rats weighing 250–290 g were kept seven to a cage at about 22°C in a light/dark cycle in which the light was kept on for 12 h from 0700. The experiments were carried out in the forenoon. The rats had free access to standard pellet food and tap water.

The animals were allocated at random to four groups of seven rats. Two of the groups received haloperidol (Orion Pharmaceutical Co., Helsinki; 1.0 mg/kg, subcutaneously) given daily for 3 weeks to cause a 'chronic' blockade in the striatal dopamine receptors. The two other groups, receiving saline, served as controls. During the 3 weeks the mean weight increase was 13 g in the haloperidol-treated rats and 33 g in the controls.

After a withdrawal period of 3 days oral sensory stimulation was applied to the first haloperidol-treated and the first saline-treated groups. On the following day the same groups were given an apomorphine injection, and the oral stimulation was renewed. After withdrawal periods of 6 and 7 days identical treatment was given to the second haloperidol-treated and the second saline-treated groups. A randomized group of seven rats taken from the two haloperidol-treated groups was also tested for the effect of oral stimulation after a withdrawal period of 28 days.

For the apomorphine injections, given to stimulate the central dopamine receptors, apomorphine hydrochloride (Europ. Ph.) was freshly prepared in saline with an antioxidant. A dose of 1.0 mg/kg (calculated as the base) was injected subcutaneously.

Oral sensory stimulation was applied by fixing an acrylic cap on the lower incisors, to interfere with the occlusal balance (20). The caps were mounted under ethyl ether anesthesia. When the rats had regained the righting reflex, apomorphine was given, and the 2-h observation period began.

Oral stereotypy and bruxism were recorded at 15-min intervals. Observations made at the recording time ± 5 min were included in the results. The rating was based on audible and visible changes in oral behavior made independently by two observers (20). In the scale used for rating, the strength of the response increased from grade 0 to 6.

Oral dyskinesias:

Stereotypy	1. Sniffing (and exploratory behavior) 2. Mouth opening and licking of cap and cage walls 3. Occasional snapping of cage walls 4. Biting of cage walls
Experimental bruxism	5. Periodic grinding of teeth and cap 6. Continuous clicking or static clenching of teeth and cap

The sum of the highest grades reached in the group of seven rats at a certain time is given in the results. When the cap–apomorphine stimulation was used, the stereotypy appearing before the bruxism usually comprised only grades 1 and 2. This is indicated by 'sniffing & licking' in the figures.

Statistical treatment. The Friedman two-way analysis of variance using ranks was taken as the nonparametric test. Since the components of the oral dyskinesias are dependent on each other, and the variable increases in intensity on an ordinal scale, it also seemed to be justified to verify the difference with Student's paired *t* test.

Results

After the 3-week exposure to haloperidol and a withdrawal period of 3 days, functional supersensitivity of the central dopamine receptors could be demonstrated by subjecting the rat to oral sensory stimulation *alone*. The rats pretreated daily with haloperidol had a significantly higher bruxism score than the rats pretreated with saline ($p < 0.01$, Friedman test; Fig. 1).

The increase in sensitivity to oral sensory stimulation lasted for 6 days at least; the response of the supersensitive group (Fig. 2) was significantly more dyskinetic than that of the control group (Fig. 1) ($p < 0.01$, Friedman test). Four weeks after the cessation of the drug treatment, no significant difference between the test group (Fig. 2) and the control group (Fig. 1) could be observed.

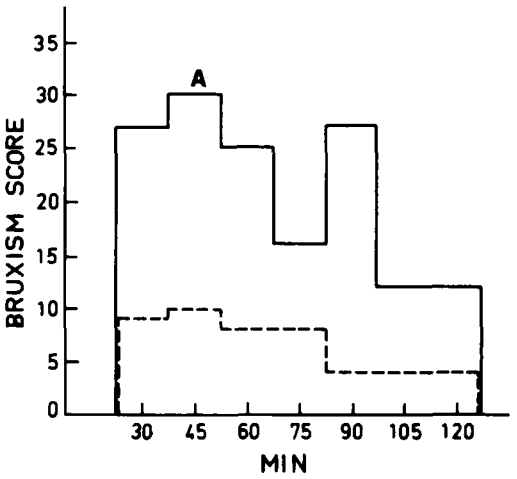

Fig. 1. Bruxism induced by an incisal cap after 21-day haloperidol pretreatment (1.0 mg/kg/day, subcutaneously) followed by 3-day withdrawal (A). Ethyl ether sedation. Saline pretreatment (broken line). No. = 7.

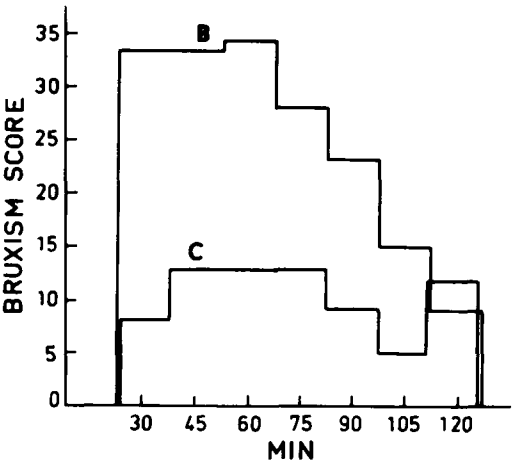

Fig. 2. Bruxism induced by an incisal cap after a 21-day haloperidol pretreatment followed by 6-day (B) and 28-day (C) withdrawal periods. No. = 7.

After a withdrawal period of 4 days the oral sensory stimulation was combined with injection of apomorphine. Stereotypic oral dyskinesias—that is, sniffing and licking—together with enhanced locomotor activity predominated over bruxism during the early part of the 2-h test period (Fig. 3). A similar delay in the peak response of bruxism was seen even more clearly after the 7-day withdrawal (Figs. 2 and 4).

Few oral stereotypies were observed during the terminal part of the 2-h test period or during the most intense bruxism period (Figs. 3 and 4). The supersensitive rats generally reacted more intensely to the cap–apomorphine stimulation than the rats pretreated with saline (e.g. at 90 min in Fig. 4). However, with the cap–apomorphine stimulation the *total* bruxism response was weaker than with the oral sensory stimulation alone (haloperidol-pretreated rats, Figs. 2 and 4; $p < 0.05$, *t* test).

Discussion

The dopaminergic receptors of the rat brain were sensitized by haloperidol treatment for the purpose of disposing the animal to oral dyskinesias. The main result of the experiments with these sensitized rats was an increase in the frequency and intensity of

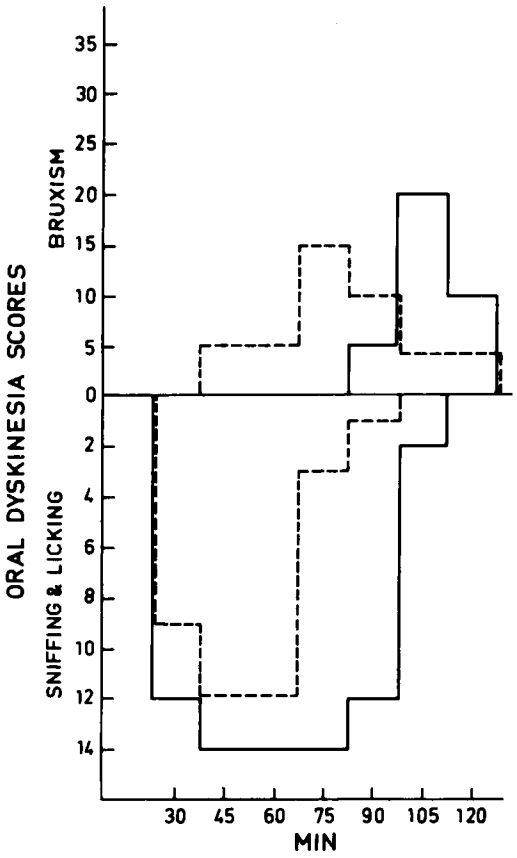

Fig. 3. Oral dyskinesias induced by cap/apomorphine (1.0 mg/kg, intraperitoneally) treatment after a 21-day haloperidol pretreatment (1.0 mg/kg/day, subcutaneously) followed by a 4-day withdrawal (unbroken line). Ethyl ether sedation. Saline pretreatment (broken line). No. = 7.

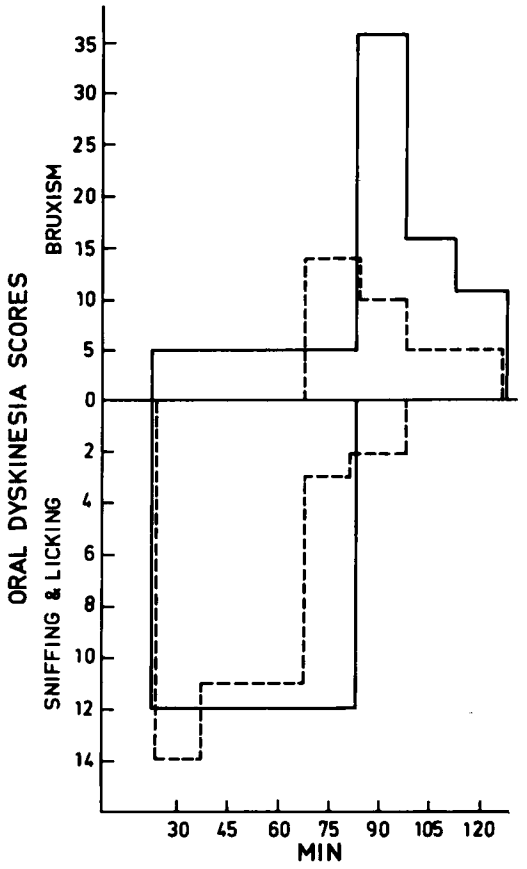

Fig. 4. Oral dyskinesias induced by cap/apomorphine (1.0 mg/kg, intraperitoneally) treatment after a 21-day haloperidol pretreatment followed by a 7-day withdrawal period (unbroken line). Saline pretreatment (broken line). No. = 7.

bruxism-like responses caused by oral sensory stimulation *alone*. Sensory impulses, discharged by mechanical interference, initiated oral dyskinesias, which were facilitated by sensitization of the dopamine pathways in the brain. Sensory impulses are known to cause release of dopamine in the nigrostriatal system (15).

In synaptic functioning, dopaminergic neurotransmission appears to be dynamically modulated by both pre- and post-synaptic feedback mechanisms (5, 26). The dopamine turnover is regulated physiologically by the presynaptic receptors or autoreceptors; stimulation causes decrease in dopamine production (14). When the presynaptic receptors are blocked, loading of the presynaptic nerve terminals occurs. Moreover, the postsynaptic receptors become sensitized when the neuron is not firing normally (2).

When the haloperidol-induced postsynaptic blockade is abolished, some of the neurolept continues to block the presynaptic receptors (7). Functional supersensitivity develops and becomes apparent when the cumulated presynaptic dopamine stores are released by sensory stimuli. The dopamine that is released affects the sensitized postsynaptic receptors, and an exaggerated oral response is seen.

In the second part of the experiment the

sensitized dopamine receptors were also stimulated by the dopaminergic agonist apomorphine. Stereotypic behavior with sniffing and licking predominated, before dyskinesia with exaggerated tooth gnashing appeared. There seemed to be competition between the stereotypy and bruxism-like response. Apomorphine-induced behavioral competition has been described earlier by other investigators (22). It has been suggested that low doses of apomorphine (0.05–0.1 mg/kg) may directly inhibit the firing of dopaminergic presynaptic neurons (1, 4, 7). This situation may prevail during the latter part of the experiment, when the apomorphine begins to be depleted. The fact that the presynaptic receptors had been sensitized by haloperidol may explain why apomorphine did not increase the dyskinetic response induced by sensory stimulation, as it did in our experiments without receptor sensitization (25).

Various types of peripheral sensory stimulation augment the release of dopamine in the nigrostriatal pathway of the feline brain (15); thus oral sensory stimulation may facilitate the release of striatal dopamine as well. Study of the factors related to the induction of acute oral dyskinesias by dopaminergic stimulation in the rat (19, 20) suggested the importance of oral sensory stimulation and stress. Occlusal interference and psychic stress, e.g. aggression, are regarded as strong etiologic factors in human bruxism also (8, 16, 21). For these reasons, the combination of oral sensory stimulation and central dopaminergic hyperfunction in the rat was introduced as an animal model for human bruxism (20). Now it appears that sensory stimulation also has a role in the induction of experimental TD.

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