# Experimental aggression and bruxism in rats

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Aggression has been suggested as one of the etiologic factors in bruxism. Experimental bruxism, audible, nonfunctional grinding or clenching of the teeth, was provoked in aggressive animals by drugs affecting central dopaminergic systems. Electric foot-stimulation was used to induce aggression, evident as the threatening or fighting position, in paired male Wistar rats. After initial stimulation, shocks were given only to maintain the characteristic fighting pose. Apomorphine facilitated induction of aggressive behaviour by electric shocks, and the rats receiving both treatments showed bruxism more frequently than controls subjected to shocks alone: up to 95 bruxism periods registered by a tape recorder during 30 min, as opposed to a few sporadic periods in the controls. Without shocks, apomorphine-treated rats displayed stereotypy with locomotion and biting of various objects. Aggression and bruxism were not equally successfully induced after L-dopa given with a peripheral inhibitor of aromatic amino acid decarboxylase (benserazide) or when L-dopa treatment was modified with the inhibitor of dopamine-β-hydroxylase (diethyldithiocarbamate) or monoamine oxidase inhibitor (iproniazid). However, all the present drug combinations known to enhance central dopaminergic function seemed to increase irritability and disposition to experimental oral dyskinesias. This was observed especially when a sensory stimulus was applied at the same time or the drug had an amine-releasing effect (pheniprazine).

*Key-words:* Dopaminergic drugs; oral dyskinesias; stereotypy

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## *Aggression and bruxism in man*

It is not known why nonfunctional clenching and grinding of teeth occurs, but a dual etiologic background of psychic stress and occlusal disharmony has been widely accepted (27). Changes in an emotional state are reflected by muscle tension in general and by tension of the masticatory muscles in particular (5, 24, 31).

Psychic stress or emotional tension, including aggression, anger, hostility, anxiety and fear, has been discussed in several papers dealing with bruxism. Aggressiveness has been claimed to form the psychic background of bruxism (13, 35, 36, 45, 46), but negative findings have also been reported (14, 21).

Bruxism seems to be a multifactorial phenomenon, since the etiologic significance of occlusal interference is indisputable (27). Using psychological tests and questionnaires, Olkinuora (23) could divide bruxists into a mental strain group and a non-strain group. The strain bruxists were aggression-releasing, anxious and more tense.

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*Central amine transmitters and aggression*

The role of brain neurotransmitters in aggressive behaviour has received much attention and several of the known transmitters have been implicated. Changes in the amount of amines or turnover of monoamine transmitters are supposed to be related to affective aggressiveness in animals, because this behaviour can be modified by drugs influencing these amines (43).

Several investigators relate the increase in aggressive behaviour to an increase in the brain dopamine. The direct precursor of dopamine, L-dopa, enhances fighting in experimental animals (12, 39), and drugs blocking dopamine receptors effectively inhibit aggression in various laboratory models (18, 43). Correspondingly, a dopamine-mimicking agonist, apomorphine, induces aggressive behaviour in rats (15, 30, 42). Finally, some patients who receive excessive treatment with L-dopa in Parkinson's disease exhibit increased arousal and irritability (2).

In studies of aggression dopamine has aroused great interest, but on the other hand the increase of brain serotonin is supposed to facilitate experimental induction of fighting behavior (1) and noradrenaline may be involved in the production of rage behavior, while dopamine plays a minor role (16). The function of monoamines or other transmitters in aggression is still unclear and it is possible that features of aggression are produced by disturbances of the balance between transmitter systems in the brain.

*Drug-induced experimental bruxism*

The fundamental reflexes of jaw-closing and jaw-opening are influenced by interneurones in descending paths from the cerebral cortex to the trigeminal motor neurones. The hypothesis that oral movements have a cortical origin suggests a "rhythm generator", which interacts with various oral reflexes and which can be switched on either by activity in higher centers or by sensory stimuli in the mouth (37). The role of dopamine in the interrelation of emotional behaviour and oral reflexes is of special interest, since dopamine is richest in the striatum and substantia nigra, which form part of the extrapyramidal system. The system integrates and refines motor activity. The function of dopamine in this system may be of crucial importance for the intense motor activity in aggression, including nonfunctional masticatory movements. A neuropharmacological approach to experimental bruxism showed that an animal model for this motor dysfunction can be demonstrated on a dopaminergic basis (26).

In the present study, the significance of aggressiveness in drug-induced bruxism is studied by using electric stimulation to induce aggression in rats.

## MATERIALS AND METHODS

Male Wistar rats weighing between 300 and 400 g were kept 12 to a cage at 22 °C with a light/dark cycle in which the light was kept on from 07.00 to 19.00 hours. The animals had free access to tap water and pellet food was available until the evening before the experiment-day, when they were housed singly in a dark, sound-proof room. Cross over arrangements were used in the aggression and stereotypy tests with drug combinations. It was hoped that this levelled off the variation in aggressiveness between individuals, observed, for instance, during the handling of the rats. About 4 weeks were allowed to lapse before the reuse of an animal (maximum three times).

*Aggression*

Drug-induced aggression was measured by placing two rats in a test chamber

(29 x 25 x 25 cm) with a transparent front panel. After drug treatment they were observed for 30 min, and attacks and bites of one rat by the other, and periods spent in a threatening posture (fighting pose) were recorded. In the results, aggression is considered to be achieved if the drug induced at least one fighting period. In addition, subjective estimates were made of detectable autonomic and skeletal-facial responses (e.g. piloerection, masseter tremor) and vocalizations.

Electric shock-induced fighting was provoked by foot shocks given through a grid floor in the test chamber. The stimulator unit contained a power supply, a constant alternating current source and a timing circuit. After preliminary experiments, a pulse intensity of 2.2 mA with a duration of 0.5 sec was chosen. Before testing, the feet of the rats were dipped in a glycerol-saline solution. The initial shocks were given every 10 sec until the pair assumed the fighting pose (usually 2–5 shocks in controls). Thereafter the shocks were given only when the pose and fighting ceased. These later shocks were counted for the results. The controls always needed more than 30 shocks for a 30-min pose. If 10 or fewer shocks were needed (after initial shocks) to maintain aggression for 30 min in drug-treated animals, the drug was considered to facilitate shock-induced fighting. The disappearance of facilitation was checked 2 weeks after drug treatment.

Originally, a "motivated aggression model" of Burov (4) was included in the experimental procedure. The rats were trained singly to avoid foot-shocks by jumping onto a small bench. Avoidable foot-stimulation of two male Wistar rats in the cage led not to joint escape onto the bench (as in the females), but to continuous fighting. Usually, neither of the rats occupied the bench, but both assumed the fighting pose (Fig. 1). However, the results showed no difference

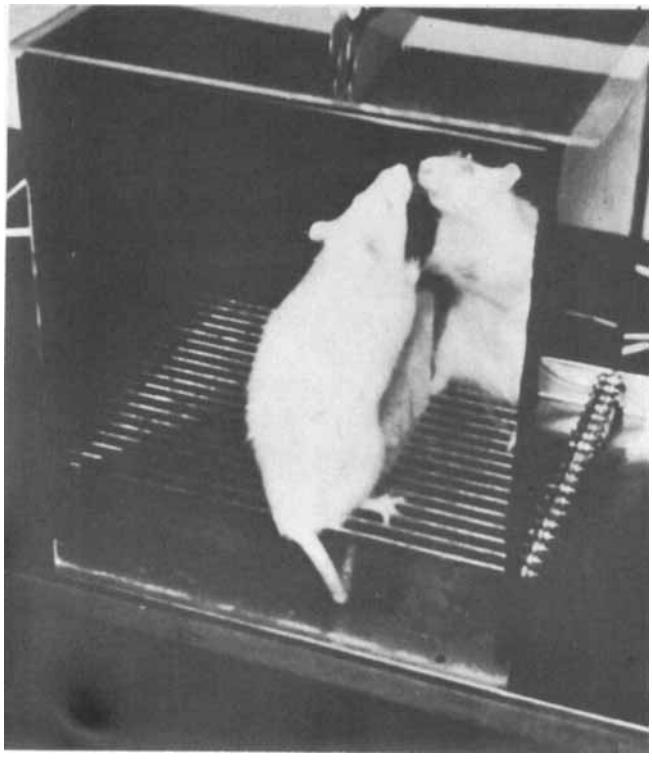

Fig. 1. Experimental aggression was provoked by electric foot-stimulation through a grid floor in a transparent chamber. Two male Wistar rats in a fighting pose typical of those during which bruxism periods were recorded by a tape recorder.

when avoidable stimulation (bench present) or unavoidable stimulation (no bench) was used, and the motivated aggression model was employed only in the experiments with apomorphine.

*Stereotypy*

Single rats were rated for stereotypy according to the scales described earlier (26). Exploratory behavior, even without biting, was recorded as a positive response.

*Bruxism*

Clenching and grinding of teeth were regarded as a model for human centric and eccentric bruxism. Biting of an object, e.g. the grid floor, was not taken as bruxism. Bruxism was recorded with a tape recorder for 30 min after drug treatment. A microphone was placed in the test chamber with the aggressive animals. The total number of bruxism periods occurring in two rats could thus be counted from recordings. A few (1–3) sporadic periods of bruxism were not taken as a positive response, but frequent bruxism (usually 20–60 periods/30 min) was required for this.

*Drugs and timing*

Intraperitoneal apomorphine injections of 2.5–20.0 mg/kg were given 10 min before the 30-min observation period began.

L-dopa, 50 or 150 mg/kg, i.p., was administered 60 min and benserazide, 50 mg/kg, s.c., 45 min before the observation period.

Diethyldithiocarbamate (DDC) 500 mg/kg, s.c. was given three times: 24, 6 and 3 hours before the observation period.

Monoamine oxidase inhibitor iproniazid, 100 mg/kg, s.c., was given 4 hours before L-dopa or 5 hours before the observation period, and pheniprazine, 5 mg/kg, s.c., twice: 24 hours and 30 min before the observation period.

The drugs used were: apomorphine hydrochloride (Ph. Nordica), freshly prepared in saline containing 0.1 % sodium pyrosulphite as an antioxidant, L-dopa methylester (Labkemi, Gothenburg), benserazide hydrochloride (Ro 4–4602, Hoffmann-La Roche & Co, Basle), sodium diethyldithiocarbamate trihydrate (E. Merck, Darmstadt), iproniazid phosphate (Hoffmann-La Roche, Basle) and pheniprazine (beta-phenylisopropylhydrazine, Draco AB, Lund). The doses refer to the bases. All the experimental series comprised 10 rats or 10 rat pairs.

## RESULTS

The largest dose of apomorphine (20.0 mg/kg) induced fighting without electric shocks in 40 % of the rat pairs and all these pairs showed a low-frequency bruxism response, viz 6–10 bruxism periods/30 min (Table 1, I). Apomorphine clearly facilitated shock-induced aggressive behavior (Table 1, II). When large doses of apomorphine (10.0 and 20.0 mg/kg) were given, several (5–15) initial shocks were needed to provoke fighting; but once the fighting pose was assumed, threatening with attacks lasted for 30 min without any further shocks in 12 out of 20 rat pairs. In saline controls the fighting pose was assumed with fewer initial shocks than with apomorphine, but continuous shocks were needed to maintain aggression.

All the fighting rats in which aggression was facilitated by apomorphine showed frequent bruxism, up to 95 bruxism periods/30 min being counted. In contrast, few sporadic teeth-clenching periods were registered in controls. The doses of 2.5 and 5.0 mg/kg of apomorphine also induced bruxism during the facilitated aggression, but in 60 % of the rat pairs receiving the smaller dose no facilitation was observed and bruxism appeared only sporadically.

Table 1. *Percentage responses in aggression, stereotypy and bruxism after apomorphine injection*

| Treatment | | Aggression[1] | | Stereotypy[2] | Bruxism during | | |
|---|---|---|---|---|---|---|---|
| | | I | II | III | | | |
| Drug | mg/kg i. p. | Drug-induced fighting | Facilitation by drug of shock-induced fighting | Locomotion, biting | I | II | III |
| Saline | – | 0 | 0 | 0 | – | – | – |
| Apomorphine | 2.5 | 0 | 40 | 80 | – | 40 | 0 |
| » | 5.0 | 0 | 100 | 100 | – | 100 | 0 |
| » | 10.0 | 0 | 100 | 100 | – | 100 | 10 |
| » | 20.0 | 40 | 100 | 100 | 40 | 100 | 40 |

[1] Rats in pairs, all the series included 10 rat pairs
[2] Single rats, all the series included 10 rats

Table 2. *Percentage responses in aggression, stereotypy and bruxism after treatment with drugs affecting monoamine levels in the brain*

| Treatment | | Aggression[1] | | Stereotypy[2] | Bruxism during | | |
|---|---|---|---|---|---|---|---|
| | | I | II | III | | | |
| Drugs | mg/kg | Drug-induced fighting | Facilitation by drug of shock-induced fighting | Locomotion, biting | I | II | III |
| Saline | | 0 | 0 | 0 | – | – | – |
| L-dopa/B[3] | 150 | 0 | 80 | 20 | – | 70 | 0 |
| L-dopa/B + DDC[4] | | 0 | 40 | 0 | – | 0 | – |
| L-dopa/B + iproniazid | 100 | 20 | 0 | 100 | 0 | – | 10 |
| DDC | | 0 | 0 | 0 | – | – | – |
| Iproniazid | | 0 | 100 | 0 | – | 60 | – |
| DDC + iproniazid | | 10 | 100 | 0 | 0 | 100 | – |
| DDC + pheniprazine[5] | | 80 | 100 | 40 | 80 | 100 | 0 |
| Pheniprazine | | 0 | 100 | 100 | – | 100 | 0 |

[1] Rats in pairs, all the series included 10 rat pairs
[2] Single rats, all the series included 10 rats
[3] B = benserazide (50 mg/kg) as a peripheral inhibitor of aromatic amino acid decarboxylase
[4] DDC = diethyldithiocarbamate 500 mg/kg three times during 24 hours, as an inhibitor of dopamine-β-hydroxylase
[5] Pheniprazine 5 mg/kg twice during 24 hours, as a monoamine oxidase inhibitor and a catecholamine-releasing agent

In the single rats, apomorphine injections induced stereotypy in the form of exploratory behavior, sniffing, licking and biting of the cage wires (Table 1, III). After the two largest apomorphine doses, periods of stereotypic biting were observed in all the single rats and bruxism was recorded during these periods in half of the rats. Compulsory biting of objects was also seen in paired, fighting rats, but only when the experimenter interrupted the fighting.

After treatment with 150 mg/kg of L-dopa facilitation of shock-induced aggression and simultaneous bruxism were recorded in 70 % of the rat pairs (Table 2). Without shocks only weak stereotypy was observed, consisting of exploratory behavior.

The inhibition of dopamine-β-hydroxy-

lase by pretreatment with diethyldithiocarbamate (DDC) reduced aggression induced by shocks and L-dopa, and abolished bruxism. A sedative effect was evident, especially when DDC was given alone.

When monoamine oxidase was inhibited by iproniazid, the fighting response could not be induced by the shock-L-dopa treatment, although all the rats showed stereotypy. After iproniazid alone no stereotypy was seen, but when shocked in pairs all the rats behaved aggressively and in six out of ten pairs bruxism was recorded.

Iproniazid given to DDC-treated rats enhanced readiness to aggression. Notwithstanding the DDC sedation, usually only a few shocks or knocking on the cage wall was needed to provoke a furious attack with bruxism. When another type of monoamine oxidase inhibitor, pheniprazine, was given with DDC, drug-induced aggression appeared in 80 % of the rat pairs observed in undisturbed conditions. With pheniprazine + DDC fighting started after about 30 min, i.e. several hours earlier than the response to iproniazid + DDC. Stereotypic locomotion was seen after the administration of pheniprazine, but not after iproniazid.

## DISCUSSION

Chemical or electrical stimulation, brain lesion or isolation of animals can be used to elicit aggressive response (43). Electrical paw stimulation was chosen for this study because it allowed a simple experimental design and because it is probable that the central dopaminergic systems are involved, for instance this has been indicated by experiments with haloperidol. This dopamine receptor blocker reduces aggression induced by paw shocks in paired rats (18). Adaptive kinetic changes in the neuronal uptake of striatal dopamine take place in an immediate response to shock-induced fighting (17). Dopamine neurons may respond to shocks and to increased firing by increased uptake of dopamine, but the activation of the dopaminergic systems by foot shocks has also been shown to vary (38).

The present study provided evidence that dopaminergic mechanisms are involved in shock-induced aggression and concomitant bruxistic behavior. Apomorphine, a dopamine agonist, facilitated aggression and bruxism. Earlier results show that large doses of apomorphine can provoke aggression, which can be inhibited by haloperidol (18, 30) and that apomorphine can provoke bruxism in the rat (26). The present results suggest that apomorphine and electric shock treatment had an additive effect in inducing both types of behavior. It is not known why apomorphine-treated rats needed more initial shocks than the controls before the onset of fighting. One possibility is that apomorphine affected not only postsynaptic receptors of the dopamine neuron, but also presynaptic receptors. A dopaminergic neuron seems to be subject to inhibitory feedback regulation via presynaptic receptors (11). Bunney & Aghajanian (3) have shown that the administration of apomorphine can lead to a decrease in the firing rate of dopamine neurons. Another explanation is competition between two stereotyped behaviors (40). In the initial phase, gnawing may be prepotent over the attack behavior.

It is also uncertain why the typical masticatory effects of apomorphine in the single rat, i.e. eccentric gnawing or grinding, are changed to centric clenching of teeth in an aggressive rat pair. Although this pattern predominates, sudden clenching periods can occur during the stereotypic gnawing in single rats, and if threatening behavior is forcibly interrupted in a pair, the rats can grind their teeth or gnaw any object in the cage.

The treatment of Parkinsonism with L-dopa often provokes oral dyskinesias (2), which sometimes include deleterious bruxism (19). In addition, dopamine and

precursor L-dopa are connected with aggressive behavior (see introduction). We found that L-dopa given with benserazide did not cause spontaneous fighting in rats, but facilitated shock-induced aggression and induced concomitant bruxism. The dose of L-dopa given with benserazide, which favours formation of central catecholamines (6), was fairly large, 150 mg/kg. However, the lower dose of L-dopa, 50 mg/kg, was ineffective. Thoa et al. (40) have reported vigorous spontaneous fighting in rats given L-dopa (100 mg/kg) and peripheral decarboxylase inhibitor after the development of denervation hypersensitivity in the dopaminergic pathway in the brain.

Although it is likely that L-dopa was converted mainly to dopamine rather than to noradrenaline (6), an effort was made to enhance the dopaminergic induction of aggression and bruxism by further increasing the dopamine load of the neurons involved. Diethyldithiocarbamate (DDC) inhibits the synthesis of noradrenaline from dopamine by blocking the enzyme dopamine-β-hydroxylase (8). Dopamine can also be increased after L-dopa treatment by inhibiting monoamine oxidase. The accumulation of dopamine then being greater than that of noradrenaline (20). The reason may be that monoamine oxidase inhibitors of hydrazine type, like iproniazid, also inhibit dopamine-β-hydroxylase.

Pretreatment with DDC before administration of L-dopa reduced facilitation by L-dopa of shock-induced fighting and abolished bruxism. The weakening of the response, instead of its potentiation, may be explained by the marked central nervous depression caused by DDC (7). The sedative effect was also clear when DDC was given alone, although the animals were easily aroused by a disturbance.

The effect of pretreatment with iproniazid was also unexpected. Iproniazid causes behavioral excitation or depression depending on the animal species, the dose and the consequent alterations in the central transmitter balance (34). Iproniazid alone (100 mg/kg) caused no excitation or stereotypy, but when combined with L-dopa (150 mg/kg) it resulted in continuous sniffing, licking and moving in all the rats. The excitation was reflected in some spontaneous fighting, and fighting could also be provoked by sensory interference e.g. noise or knocking on the cage. More intense sensory stimulation, viz electric shock, failed to evoke aggression possibly because it caused an immediate toxic response. The rats became clearly exhausted and the shocks were discontinued. Reduction of the dose of L-dopa or iproniazid abolished the spontaneous excitation.

In spite of the sedative effect of DDC, striking contrasting aggression was reported when it was given together with the monoamine oxidase inhibitor pargyline (29). As iproniazid alone facilitated shock-aggression and induced concomitant bruxism, it was tried in combination with DDC. Disappointingly, the results obtained with pargyline could not be reproduced with iproniazid; only one pair of rats fought spontaneously, but knocking on the cage or a single shock started fighting and vigorous tooth clenching in otherwise sedated rats. This draws attention to the difference between iproniazid and pargyline. Many monoamine oxidase inhibitors (e.g. pargyline) and particularly those with a phenylisopropyl moiety (e.g. pheniprazine) produce amphetamine-like stimulation independent of their enzyme-inhibiting activity (9). Amphetamine is known to release catecholamines in the brain. The difference in the results may have been caused by a dopamine-releasing effect in pargyline due to its structural similarity to amphetamine, a character which is lacking in iproniazid.

It appeared that DDC + pheniprazine was the only drug combination in this study which could provoke consistent aggression and bruxism. The explanation that pheniprazine released catecholamine stores is supported by the fact that the responses

could only be demonstrated on the following day, after the second injection of pheniprazine, obviously because enzyme inhibition develops several hours after the amphetamine-like effect of the first dose has ceased (25). However, this does not explain the difference from the response obtained with pargyline, since aggression then began 4–5.5 hours after only one injection (29). The results with pargyline may be ascribed to monoamine oxidase inhibition, rather than to a releasing effect, which occurred within 30 min with pheniprazine.

To summarize, drug treatments known to enhance the catecholamine and especially the dopamine load or receptor stimulation in the extrapyramidal system seemed to increase excitation of aggressive behavior and the disposition to oral dyskinesias. Remarkably, a sensory stimulus like a paw shock, knocking on the cage or a monoamine-releasing drug was usually needed for the initiation of hostility and bruxism responses.

Interest attaches to the connection between sensory inputs and the initiation and maintenance of repetitive, uncontrolled oral behavior induced by dopaminergic hyperfunction. A great number of vertebrates from mice to man behave quite similarly in this respect, e.g. farm animals like the pig, calf and sheep develop a furious desire for oral sensory inputs during dopaminergic stimulation, but they prefer snout-rubbing, licking and gnawing, respectively (10, 32). Is it the most rhythmic or primitive reflex of a species which first becomes involved? Does a link exist between these observations and the involvement of occlusal interferences in the etiology of bruxism? The treatment of patients with bruxism should include careful attention to occlusal adjustment; there are patients who are apt to develop "occlusal neurosis" and oral dysfunctions when adjustment is faulty (28). The results recently obtained by Nieoullon et al. (22) with cats indicate that nigrostriatal dopaminergic neurons are involved in the integration of various sensory inputs and that the extrapyramidal system plays a role in sensory-motor co-ordination.

Although consistent parallelism was demonstrated between experimental aggression and bruxism in this study, it must be stressed that a behavioral study gives no idea of the brain structures involved. The dopamine nerve terminals in the rat amygdala seem to be an extension of the dopaminergic neurons of the striatum (41). The amygdala is among the limbic structures regulating aggressive behavior, but the amygdala also regulates somatic functions, such as motor facilitation or inhibition (44). Thus, the nigrostriatal pathway and/or amygdala or other related structures, especially the hypothalamus, may participate. Nor is it clear whether this experimental bruxism is a consequence of the aggressive reaction or its parallel due to dopaminergic hyperfunction in different brain nuclei.

The fact that rhythmic jaw activity can exist in decerebrated mammals does not mean that oral functions in intact animals are not influenced by the higher centers of the brain. Sensory stimuli are needed for the "reflex chain" explanation of rhythmic jaw activity (33), and the "cortical" concept of the origin of oral movements does not exclude modification of habitual or unconscious masticatory activity by sensory inflow (37). Studies are needed on oral behavior when treatment with drugs affecting the dopaminergic and related neuronal pathways in the brain is accompanied by occlusal sensory interference.

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