Influence of central dopaminergic and oral sensory stimulation on the tone of the rat masseter muscle

Birgitta Sundén-Kuronen, Pentti Pohto and Erkki Alanen
Department of Pharmacology, University of Helsinki, Helsinki, Finland

Sundén-Kuronen, B., Pohto, P. & Alanen, E. Influence of central dopaminergic and oral sensory stimulation on the tone of the rat masseter muscle. *Acta Odontol. Scand.* 1983, 41, 159–166. Oslo. ISSN 0001–6357.

Dopamine neurons in the nigrostriatal subgroup of the basal ganglia are involved in the higher control of muscle tone and repetitive movements, possibly also in the masticatory muscles. For this reason, the effect of mechanical oral stimulation in combination with apomorphine-induced stimulation of dopamine receptors in the brain was experimentally studied in the rat. The masseter muscle tone during and after anesthesia was registered. A tachograph preamplifier and a bipolar electrode were used for the recording of summated potentials from the muscle. Dopaminergic stimulation increased the muscle tone. Oral sensory stimulation alone showed a tendency to increase the masseter tone, although the increase was not statistically significant. The increase of the tone with dopaminergic stimulation is presumably due to the fact that the dopaminergic system in the basal ganglia also controls the motor function of the masticatory muscles. Several pathological conditions of the mouth region, where a dopaminergic mechanism in the facilitation and inhibition of centrally coordinated jaw reflexes is obvious or possible, are discussed. Individual variation in neuronal dopamine synthesis, uptake, or receptor sensitivity may be one of the factors determining predisposition to masticatory disturbances both in experimental and clinical conditions. □ *Oral physiology; masticatory muscles; dopamine receptors; oral dyskinesias.*

Birgitta Sundén-Kuronen, Department of Pharmacology, University of Helsinki, Siltavuorenpenger 10, SF-00170 Helsinki 17, Finland

Next to the cerebral cortex, the subcortical basal ganglia are the centers for facilitation and inhibition of motor function. Dopaminergic neurons in the nigrostriatal subgroup of the basal ganglia are involved in the higher control of muscle tone and repetitive movements (18). Descending connections from the basal ganglia to the masticatory muscles are made via the masticator nucleus of the trigeminal nerve in the pons (28). The facilitation and inhibition of the jaw reflexes are also mediated via corticotrigeminal paths (23). A failure in the central control of trigeminal motor function can lead to involuntary movements in the oral region. These include bruxism-like phenomena, such as drug-induced oral dyskinesia in man and oral stereotypy or compulsive gnawing behavior in animals (8, 19).

The abnormal muscle movements induced by a dopaminomimetic drug, like apomorphine, or a dopamine antagonist affecting nigrostriatal receptors serve as a useful model of dyskinetic and bruxism-like movements (6, 24).

Various methods have been developed for quantifying biting and grinding. Mechanical devices, vibration converted to digital pulses, and electric capacitance differences caused by mandibular movements have been used (14, 17, 22). For the present investigation it was essential to find a method for measuring the tone of the masticatory muscles. The method should allow long-term recording and parametric statistical treatment of the results. Continuous long-term recording was needed because the nocturnal occurrence of human bruxism prompted us to investigate masticatory muscle tone in rats given an anesthetic that physiologically provided an approximation to sleep.

In this study the influence of apomorphine-induced central stimulation and mechanical oral stimulation on the masseter muscle tone during and immediately after anesthesia was measured. The study was

undertaken to clarify experimentally the possible effect of central dopaminergic mechanisms on the tone of masticatory muscles.

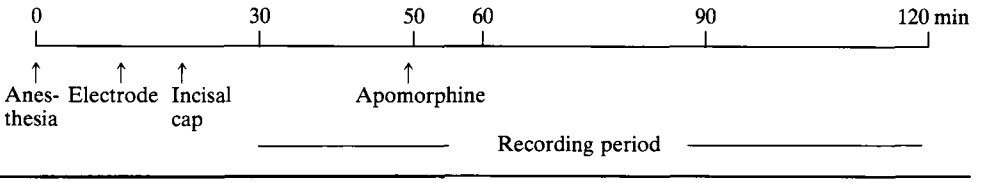
Materials and methods

Male Wistar rats weighing 200–250 g and kept in standardized conditions were used for recording experimentally induced alterations in the tone of the masseter muscle during and after anesthesia. Chloral hydrate, 250 mg/kg (50 mg/ml), was given intraperitoneally as an anesthetic.

Recording muscular tone

A method was designed in which a tachograph preamplifier was used to record summated potentials from the rat masseter muscle. The recordings were made unilaterally from the masseter muscle with a bipolar concentric electromyographic needle with a diameter of 0.306 mm (FCD 25, Medelec Ltd.). The tip of the electrode was inserted into the exposed masseter. The rest of the electrode was insulated, and an attached wire loop was sutured to the muscle. The output was fed to the tachograph preamplifier of a Grass Model 5 D Polygraph. The ground electrode was placed in the skin of the back. In the driver amplifier the half-amplitude frequency was 60 Hz. The use of a tachograph makes visually informative long-term recording possible. The exceptionally slow chart speed of 10 mm/min was used; continuous recording for 2 h is shown on only 120 cm of chart paper. The muscular tone was recorded as pen deflections triggered by summating muscular potentials. When the tone was increased, the tachograph did not give full-scale deflections. The area not covered by the ink trace was measured in terms of blank background squares on the chart paper. For the sake of clarity, the figures show the negatives of the recordings; the black spikes represent the response. Recording always began 30 min after administration of the anesthetic and lasted at least 1.5 h. The rat regained consciousness during the observation period.

The experimental schedule was as follows:



Muscular tone was modified in two different ways. Each rat of the test group of 5 rats was tested in four different treatments (20 rats in the experiments). 1) In the control experiments the only external stimulation was the presence of the recording electrode and anesthesia. 2) Additional oral sensory stimulation was given with an acrylic cap on the lower incisors (27). 3) Dopaminergic activation of the brain was caused by apomorphine hydrochloride (Eur. Ph.), 5 mg/kg intraperitoneally. 4) Combined peripheral oral and central dopaminergic stimulation was given.

Statistical significance was calculated by means of Student's paired *t* test.

Control experiments with dopamine receptor blockers

Haloperidol, 0.5 mg/kg, and domperidone, 1.5 and 3.0 mg/kg (Janssen Pharmaceutica/Orion Pharmaceutical Co.), were given intravenously 80 min after anesthetization. Both are potent blocking agents of dopamine receptors. Domperidone is a specific dopamine antagonist that does not exert haloperidol-like antidopaminergic activity in the brain, probably because it does not cross the blood–brain barrier (15, 32).

Results

Fig. 1 shows the recordings reflecting the

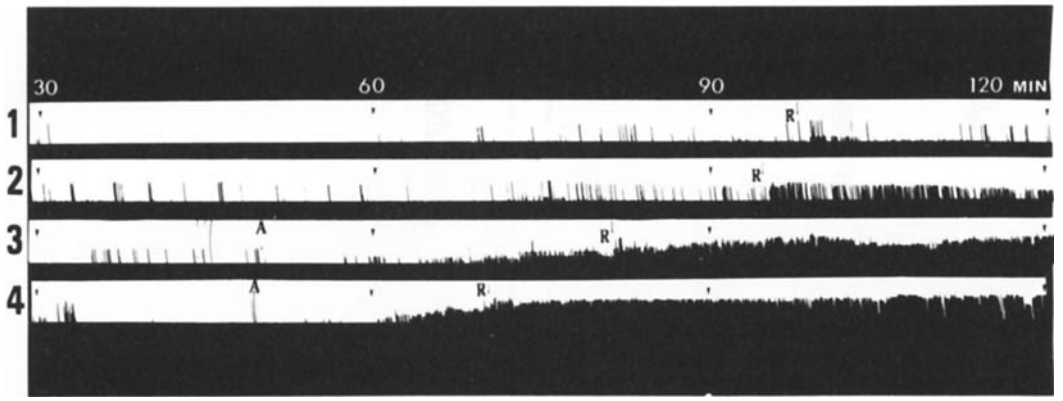


Fig. 1. A series of recordings illustrating the effect of stimulation on the tone of rat masseter muscle. 1 = Control recording; 2 = oral sensory stimulation; 3 = central dopaminergic stimulation by apomorphine; 4 = combination of peripheral and central stimulation. A = apomorphine, 5.0 mg/kg intraperitoneally; R = righting reflex appears after chloral hydrate anesthesia.

tone of the masseter muscle in the various experimental treatments. The series of four recordings is from the same rat. In all the rats, the muscle tone increased in the same manner with dopaminergic stimulation by apomorphine. Central dopaminergic stimulation always clearly enhanced the effect of peripheral sensory stimulation, except for a short period of lowered tone immediately after the administration of apomorphine. Dopaminergic stimulation caused an increase in the muscle tone even before the animals regained consciousness, but the increase in tone was especially marked after arousal.

The muscle tone during recording periods of 20 min *before and after arousal* was compared within a treatment (Fig. 2). With combined stimulation the mean value of muscular tone before arousal was 23% of that recorded for the conscious rats, and with the apomorphine treatment the corresponding value was 11%. The righting reflex (R in Fig. 1) appeared at about 1.5 h in all the four treatments.

Comparisons with the control treatment showed that oral sensory stimulation alone did not significantly increase masseter muscle tone when the records *before or after* the righting reflex were considered (Fig. 3). When the responses during the *total* recording time (open and hatched columns added in Fig. 3) are compared, however, a clear tendency to increased tone is seen with sensory stimulation alone.

With dopaminergic stimulation the tone was significantly increased ($p < 0.01$). With combined stimulation the corresponding increase was even clearer ($p < 0.001$), but there was no statistically significant difference between the records for these two treatments.

The two dopamine receptor-blocking agents haloperidol and domperidone were used to inhibit the apomorphine response and thus confirmed that the effect of apomorphine was truly central. Haloperidol gave almost immediate, long-lasting relaxation of the masseter muscle. The depressive effect on the muscle tone is seen in Fig. 4. The lack of a similar response after an equipotent intravenous dose of domperidone showed that the apomorphine was acting in the brain; domperidone does not readily penetrate the blood–brain barrier. The larger dose of domperidone gave a slight inhibition of the apomorphine effect (Fig. 4).

Discussion

An experimental animal model is the only way to approach the present problem; for ethical reasons human experiments cannot be performed. The present recording

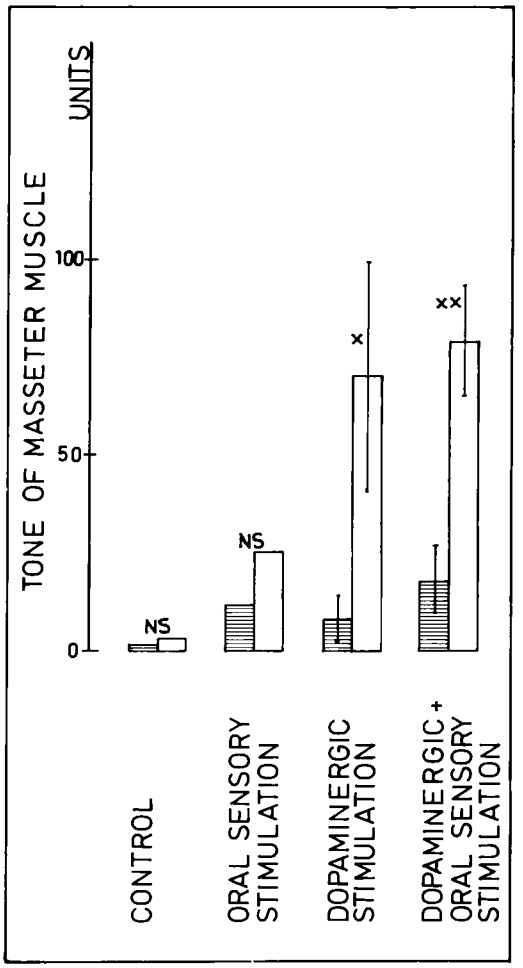


Fig. 2. Comparison of the effect of stimulation on the tone of the masseter muscle before and after arousal from anesthesia. Recording during 20 min before (hatched columns) and 20 min after (open columns) the appearance of the righting reflex. The significant difference between the hatched and open columns with dopaminergic stimulation and with dopaminergic + oral sensory stimulation shows that far-advanced arousal is a prerequisite for increase of muscle tone by dopaminergic stimulation. Means ± SD are shown. $^{**}p < 0.01$; $^{*}p < 0.05$ in Student's paired *t*-test. No. = 5. For details of units, stimulation, and anesthesia, see Materials and methods.

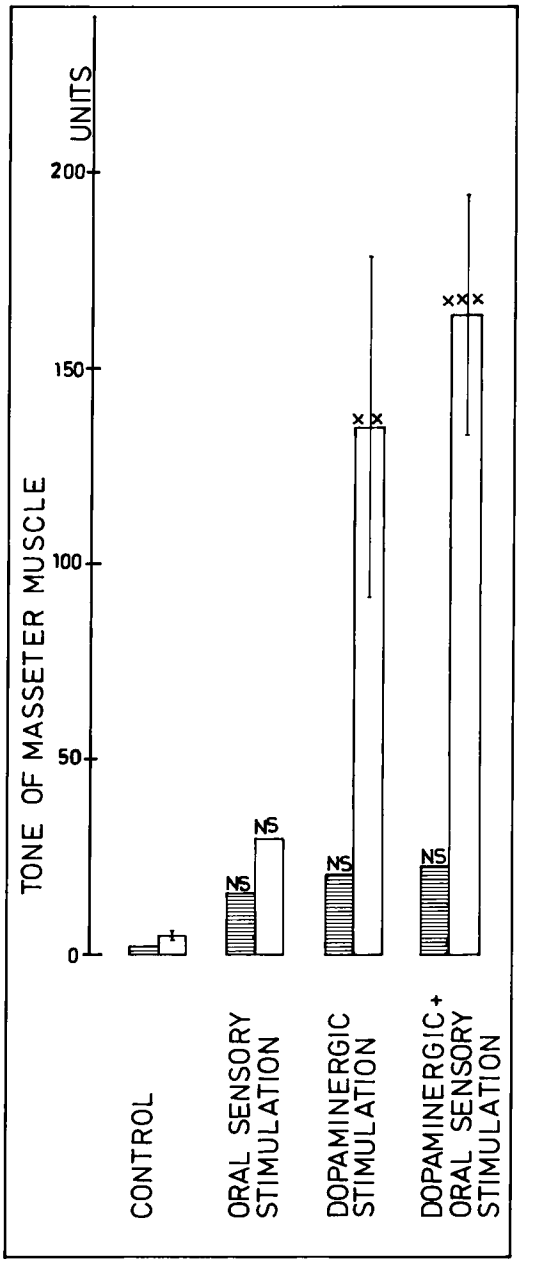


Fig. 3. The means of muscle tone in 1.5-h recordings from the masseter. Recordings before (hatched columns) and after (open columns) the appearance of the righting reflex. Dopaminergic stimulation and dopaminergic + oral sensory stimulation gave higher muscle tone than in the control treatment only after arousal from anesthesia. $^{***}p < 0.001$; $^{**}p < 0.01$ in Student's paired *t* test. No. = 5. For details of the units, stimulation, and anesthesia, see Materials and methods.

method was chosen because the tachograph preamplifier gives visually informative, long-term recording, and the slow chart paper speed gives a limited amount of data, which can be easily handled and compared. Compared with electromyography, the

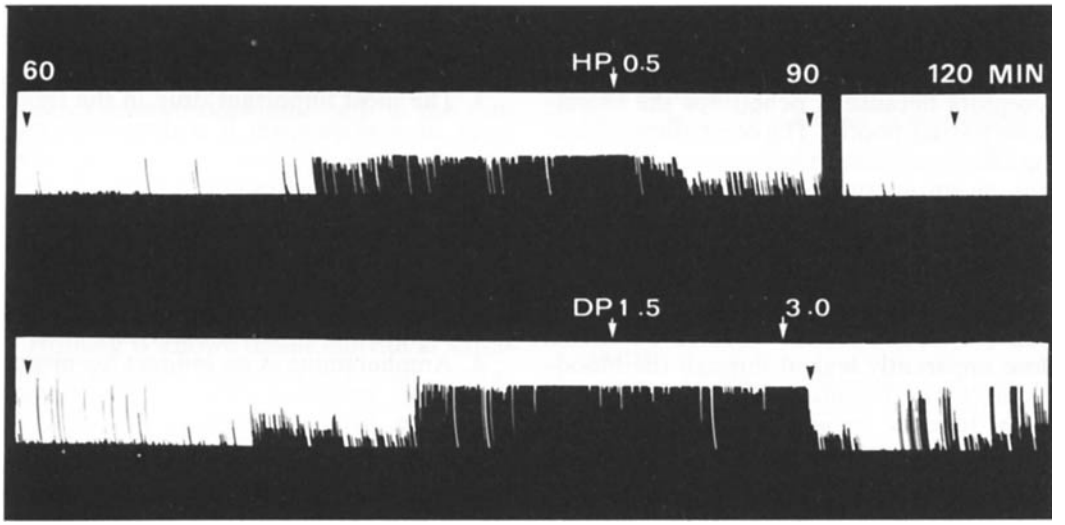


Fig. 4. Effect of the centrally acting dopamine receptor-blocking agents haloperidol and domperidone on the masseter muscle tone. The tone is experimentally increased by dopaminergic stimulation with apomorphine. The blocking effect of haloperidol (HP), 0.5 mg/kg intravenously, on dopamine receptors is seen in the first recording as a long-lasting decrease in muscle tone. In the second recording domperidone (DP), 1.5 mg/kg intravenously, does not decrease the muscle tone. An additional dose of 3.0 mg/kg gave a short-lasting response.

present method gives only a rough idea of changes in muscle tone, but in the experimental analysis of unknown factors affecting muscle tone, a general picture is of importance. Chloral hydrate anesthesia was chosen because it does not affect REM sleep and is thus more similar to natural sleep than other types (13).

The results clearly indicate that dopaminergic receptor stimulation by apomorphine causes a significant increase in the masseter tone in the conscious rat. However, the most interesting result was that dopaminergic stimulation also increased the tone before arousal from anesthesia. Bruxism periods were seen in connection with enhanced tone, but high tone was also seen without any sign of masticatory dyskinesia.

The increase of the tone of the masseter muscle with dopaminergic stimulation is presumably due to the fact that the dopaminergic system in the basal ganglia also controls the motor function of the masticatory muscles.

The influence of apomorphine is known to cease within 1 h (8), but in our experiments the level of increased muscle tone often continued unchanged after that time. The stress-provoking test conditions could be a contributory factor, but the effect of this potential factor was not evident in the control treatment.

Oral sensory stimulation without apomorphine showed a tendency to increase the masseter tone, although the increase was not statistically significant. Advanced arousal from anesthesia seems to be essential for the rat to react to mechanical stimulation in the mouth. Since a corresponding tendency was not observed in the conscious rats in the control treatment, the recording electrode alone was not responsible for this slight increase in the tone. The response to combined stimulation with apomorphine and the incisal cap shows an additive effect: both dopaminergic receptors and peripheral mechanoreceptors are involved.

Peripheral dopamine receptors also exist (32). To confirm that the dopamine receptors involved were central, the effects of two receptor blockers were compared. Domperidone and haloperidol are equipotent antag-

onists when peripheral receptors are concerned (15, 32), but domperidone has a weaker antidopaminergic effect on central receptors because it penetrates the blood–brain barrier poorly. The competitive blocking effect on apomorphine-stimulated receptors by intraperitoneally given haloperidol lasted over 2 h. However, intraperitoneally given domperidone did not change the tone when the dose was equivalent to that effective with intracerebroventricular administration (32). Some of the doubled additional dose apparently leaked through the blood–brain barrier because a decrease appeared in the tone for some minutes. These observations suggest that central dopamine receptors were involved in our study.

Olsson & Landgren (23) reported evidence of a trigemino-cortico-trigeminal path that facilitates and inhibits jaw reflexes. The characteristics of this mechanism could not be directly related to *normal* chewing. Olsson & Landgren interpret their findings as evidence of fast excitatory and inhibitory paths from the cortex to the masseteric motoneurons. Their most interesting finding was that there seems to be a switching mechanism, which can select between these two paths. Our hypothesis is that this switching mechamism lies at the subcortical level in the basal ganglia and that dopaminergic neurons are involved. It has been shown in the cat that peripheral sensory stimulation can release dopamine in the extrapyramidal system (20).

The hypothesis presented here does not rest solely on the present results. The following nine points can be regarded as further evidence:

1. Stimulation of central dopamine receptors causes aggression and stereotyped motor activity in the masticatory muscles in the rat (25). Aggression facilitates jaw closing in cats when the reflex is caused by electrical stimulation in the trigeminal motor nucleus (10). A connection has been suggested between psychic stress, e.g. aggression, and bruxism in man (21, 28).

2. The cause of parkinsonism is the constant loss of dopamine-producing nerve cells in the substantia nigra, with a consequent strong reduction of dopamine content in the striatum (4). In Parkinson's disease there is a clear motor defect in the masticatory muscles.

3. The most important drug in the treatment of parkinsonism is a dopamine precursor, L-dopa, which corrects the dopamine deficiency in the striatum. An overdose of L-dopa induces compulsory movements in the masticatory muscles (19, 29). These hyperactive, stereotype symptoms represent the opposite of parkinsonism and catalepsy in the spectrum of motor behavior.

4. Amphetamine is an indirect agonist of dopamine receptors—that is, it releases dopamine from dopaminergic nerves. In man, one of the toxic symptoms of a large dose of amphetamine is bruxism (12). Methylphenidate, a similarly acting drug, causes bruxism in monkeys with unbalanced occlusion (5).

5. The close similarity of amphetamine-induced psychosis to acute paranoid schizophrenia has been noted (2). The etiology of schizophrenia has been suggested to involve dopaminergic overactivity (7). The major group of motor dyskinesias in *untreated* schizophrenic patients is jaw movements (9).

6. When psychotic patients are *treated* with neuroleptics, which are dopamine receptor-blocking drugs, the main side effect is tardive dyskinesia, a delayed iatrogenic phenomenon emerging after long-term neuroleptic treatment, which is characterized by involuntary movements, mostly in the mouth and face region (3). These movements can be imitated in the rat by combining neuroleptic treatment with stimulation by apomorphine and occlusal interference (26).

7. In cerebral palsy (CP), dyskinesias constitute one form of handicap. The neurologic defect is of extrapyramidal origin, and thus dopaminergic mechanisms are obviously involved (1). Involuntary jaw movements and bruxism in CP patients can be intense, resulting in deleterious abrasion of the teeth (11, 16).

8. In electrophysiological experiments, Schärer (30) demonstrated experimental bruxism during stimulation in the lateral hypothalamic area, where dopamine neurons ascend to the striatum. The ablation of a specific inhibitory cortical area resulted

in a transition from rhythmic, chewing movements to tooth-gnashing.

9. In our preliminary experiments degeneration of dopamine cells in the substantia nigra prevented increase of tone in the contralateral masseter of the rat. The degeneration was induced by an intracerebral injection of 6-hydroxydopamine (31). Increase of muscle tone in anesthesia was caused by stimulation of the periodontal mechanoreceptors with veratrine.

Nothing is known about individual variation in neuronal dopamine synthesis, degradation, or uptake or in receptor sensitivity in relation to masticatory dysfunction. However, these aspects of the brain should be kept in mind when the variable susceptibility of patients to mechanical occlusal interferences is studied.

References

1. Adams, R. D. & De Long, G. R. Developmental and other congenital abnormalities of the nervous system. In: Wintrobe, M. M. ed. Harrisons's Principles of Internal Medicine, R. R. Donnelley & Sons Company, New York 1974, pp. 1849–1862
2. Angrist, B., Sathananthan, G., Wilk, S. & Gershon, S. Amphetamine psychosis: behavioural and biochemical aspects. J. Psychiatr. Res. 1974, 11, 13–23
3. Baldessarini, R. J. & Tarsy, D. Tardive dyskinesia. In: Lipton, M. A., DiMascio, A. & Killam, K. F. ed. Psychopharmacology, Raven Press, New York 1978, pp. 993–1004
4. Calne, D. B. Parkinsonism: Physiology, Pharmacology and Treatment. Edward Arnold Ltd., London 1970
5. Clark, T. D., Jr. A neurophysiological study of bruxism in the rhesus monkey. Table clinic, Am. Dent. Assoc. Annual Session. Cited by P. Schärer 1971
6. Clow, A., Jenner, P. & Marsden, C. D. An experimental model of tardive dyskinesias. Life Sci. 1978, 23, 421–424
7. Crow, T. J., Johnstone, E. C., Longden, A. & Owen, E. Dopamine and schizophrenia. In: Roberts: P. J., Woodruff, G. N. & Iversen, L. L. ed., Advances in Biochemical Psychopharmacology, Raven Press, New York 1978, 19, pp. 301–309
8. Ernst, A. M. Mode of action of apomorphine and dexamphetamine on gnawing compulsion in rats. Psychopharmacologia Berlin 1967, 10, 316–323
9. Faurbye, A., Rasch, P.-J., Bender-Petersen, P., Brandborg, G. & Pakkenberg, H. Neurological symptoms in pharmacotherapy of psychoses. Acta Psychiatr. Scand. 1964, 40, 11–27
10. Flynn, J. P. The neuronal basis of aggression in cats. In: Glass, D. C. ed. Neurophysiology and Emotions, Rockefeller University Press, New York 1967, pp. 40–60
11. Haavio, M.-L. CP-vammaiset ja hammashuolto. Suomen Hammaslääk. lehti 1972, 19, 645–652
12. Jaffe, J. H. Drug addiction and drug abuse. In: Goodman, L. S. & Gilman, A. ed. The Pharmacological Basis of Therapeutics, MacMillan, 1975, pp. 284–324
13. Kales, A., Kales, J., Scharf, M. B. & Tjiauw-Ling, T. Hypnotics and altered sleep patterns. II. All-night EEG studies of chloral hydrate, flurazepam and methaqualone. Arch. Gen. Psychiatr. 1970, 23, 219–225
14. Kubacki, A. Mandibulogram as a measure of sterotyped behavior in the rat. Psychopharmacol 1978, 59, 209–210
15. Laduron, P. M. & Leysen, J. E. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Chem Pharmacol. 1979, 28, 2161–2165
16. Lindqvist, B. & Heijbel, J. Bruxism in children with brain damage. Acta Odontol. Scand. 1974, 32, 313–319
17. Ljungberg, T. & Ungerstedt, U. A method for simultaneous recording of eight behavioral parameters related to monoamine neurotransmission. Pharm. Biochem. Behav. 1977, 8, 483–489
18. Lloyd, K. G. & Hornykiewicz, O. Catecholamines in regulation of motor function. In: Friedhoff, A. J. ed., Catecholamines and Behavior, Plenum Press, New York 1975, p. 41
19. Magee, K. R. Bruxism related to Levodopa therapy. J. Amer. Med. Ass. 1970, 214, 147
20. Nieoulluon, A., Cheramy, A. & Glowinski, J. Nigral and striatal dopamine release under sensory stimuli. Nature 1977, 269, 340–342
21. Olkinuora, M. Bruxism as a psychosomatic phenomenon. Dissertation, Univ. of Helsinki 1972
22. Olpe, H.-R. Pharmacological manipulations of the automatically recorded biting behavior evoked in rats by apomorphine. Eur. J. Pharmacol. 1978, 51, 441–448
23. Olsson, K. Å. & Landgren, S. Facilitation and inhibition of jaw reflexes evoked by electrical stimulation of the cat's cerebral cortex. Exp. Brain Res. 1980, 39, 149–164
24. Pohto, P. A neuropharmacological approach to experimental bruxism. Proc. Finn. Dent. Soc. 1977, 73, 1–13
25. Pohto, P. Experimental aggression and bruxism in rats. Acta Odontol. Scand. 1979, 37, 117–126
26. Pohto, P., Sundén-Kuronen, B. & Alanen, E. Experimental oral dyskinesias. XVI Scand. Congr. Physiol. Pharmacol., Oulu 1979. Abstr. Acta Physiol. Scand. Suppl., 1979, 78, 473
27. Pohto, P., Sundén-Kuronen, B. & Alanen, E. Effect of occlusal interference, sedation and centrally acting muscle relaxants on apomorphine-induced oral dyskinesias in rats. Proc. Finn. Dent. Soc. 1979, 75, 85–94

28. Ramfjord, S. P. & Ash, M. M. Occlusion. W. B. Saunders Co., Philadelphia 1966, pp. 23–40, 99–108
29. Rinne, U. K. & Sonninen, V. A. double blind study of L-dopa treatment in Parkinson's disease. Eur. Neurol. 1968, 1, 180–191
30. Schärer, P. Experimental bruxism in rabbits. Helv. Odontol. Acta 1971, 15, 54–57
31. Sundén-Kuronen, B. & Pohto, P. On the mediation of parodontal sensory information to the rat masseter. Joint Meeting of Divisions of the IADR, Groningen, Holland 1981, Abstr. 16
32. Willems, J. L., Bogaert, M. G. & Buylaert, W. Preliminary observations on the interaction of domperidone with peripheral dopamine receptors. Jap. J. Pharmacol. 1981, 31, 131–133

Received for publication 26 January 1982