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Yawning elicited by systemic and intrastriatal injection of piribedil and apomorphine in the rat

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Abstract. The behavioural effects of systemic and intrastriatal injections of the dopamine agonists piribedil and apomorphine in male rats were examined. Bilateral application of piribedil (50 and 100 µg) or apomorphine (5, 10 and 20 µg) to the striatum produced yawning and chewing mouth movements accompanied by intermittent stretching and sexual arousal. Low doses of piribedil (1.25 and 2.5 mg/kg) and apomorphine (0.1 and 0.2 mg/kg) injected SC produced an identical yawning syndrome. Previous work has suggested that yawning elicited by systemic dopamine agonist treatment is a consequence of dopamine autoreceptor stimulation. Similarly, the most likely explanation of the present data is that yawning elicited by systemic and central dopamine agonist treatment was due to activation of dopamine autoreceptors. Systemic injection of haloperidol and scopolamine abolished yawning induced by intrastriatal piribedil and these data provide tentative support for the proposal that a dopamine-acetylcholine link may be involved in the expression of yawning.

Key words: Yawning – Chewing mouth movements – Stretching – Sexual arousal – Piribedil – Apomorphine – Striatum

Studies on yawning and associated phenomena date back to the observation of Ferrari (1958) that intracisternal administration of the peptide hormones adrenocorticotrophic hormone (ACTH) and melanocyte stimulating hormone (MSH) produce a stretching-yawning crisis in dogs, cats, rabbits, and rats (see Ferrari et al. 1963; Gessa et al. 1967 for review). Recent pharmacological research has focussed on a syndrome elicited by various compounds in rats which consists of yawning, often accompanied by stretching and sexual arousal (Mogilnicka and Klimek 1977; Baggio and Ferrari 1983; Serra et al. 1983a, b).

We are interested in the proposal that dopamine neurones are involved in the mediation of yawning and associated responses (Mogilnicka and Klimek 1977; Holmgren and Urba-Holmgren 1980; Yamada and Furukawa 1980, 1981). Thus, low doses of the dopamine agonists piribedil, apomorphine, nomifensine, lisuride, bromocriptine, lergotrile, and L-dopa, administered systemically, produce yawning, stretching, and penile grooming in rats (Mogilnicka and Klimek 1977; Baggio and Ferrari 1983; Protais et al. 1983). At higher doses of the dopamine agonists the yawning disappears and recurrent sniffing is observed (Protais et al. 1983). This biphasic effect of dopamine agonists on yawning can be differentially modified by neuroleptic pretreatment. Low doses of neuroleptics antagonise yawning produced by 0.1 mg/kg apomorphine, whereas increasing doses of haloperidol, chlorpromazine, mezilamine, metoclopramide, and thioridazine make yawning reappear in rats injected with 0.6 mg/kg apomorphine (Protais et al. 1983).

There appears to be a relationship between dopamine agonist-induced and peptide-induced yawning. Thus, inhibition of protein synthesis by administration of cycloheximide prevents apomorphine-induced yawning and penile grooming (Serra et al. 1983a). Similarly, the lack of pituitary peptides caused by hypophysectomy abolishes yawning and penile erection induced by apomorphine (Serra et al. 1983b).

Additional evidence suggests that cholinergic mechanisms may be involved in the expression of yawning. Urba-Holmgren et al. (1977) have reported that systemic injection of the muscarinic agonists pilocarpine and physostigmine elicits yawning and stretching in infant and adult rats. The elicited responses can be inhibited by pretreatment with the muscarinic antagonist scopolamine (Holmgren and Urba-Holmgren 1980; Yamada and Furukawa 1980). It has been proposed that dopaminergic and cholinergic influences may interact to produce yawning behaviour (Holmgren and Urba-Holmgren 1980). Thus, in cross-blocking studies, it has been demonstrated that scopolamine abolishes apomorphine-induced yawning whereas the neuroleptics spiroperidol and fluphenazine potentiate physostigmine-induced yawning (Holmgren and Urba-Holmgren 1980; Yamada and Furukawa 1980).

There has been no attempt made, to date, to investigate the neural substrates of yawning and associated responses by intracranial application of drugs. The aims of the present study were threefold: first, to describe the effects of microinjection of dopamine agonists into a dopamine-rich terminal region of the forebrain on yawning and associated phenomena and on locomotor activity; second, to compare these effects with those elicited by systemic dopamine agonist administration; and third, to attempt to reverse the elicited behavioural effects by systemic injection of haloperidol and scopolamine.

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Materials and methods

1. Systemic injections

Subjects. Adult male Sprague-Dawley rats (Charles River, UK) weighing 250–350 g were used. They were housed in plastic cages with standard chow pellets and tap water continuously available. Lighting operated on a 12-h dark-light cycle (lights on 6 am.) and temperature was maintained at $20 \pm 1°$ C.

Apparatus and procedure. Testing was conducted in individual Perspex cages ($25 \times 25 \times 21$ cm) constructed in our laboratory. The rats were injected SC with saline, piribedil (1.25 or 2.5 mg/kg), or apomorphine (0.1 or 0.2 mg/kg) and immediately placed in the cages for testing without prior habituation. An observer continuously observed the animals and recorded the frequency of yawning, penile grooming, and chewing mouth movements at 10-min intervals for 60 min using a hand-held counter. Each rat was tested once only.

2. Central injections

Subjects. Adult male Sprague-Dawley rats (Charles River Canada, Montreal) weighing 250–350 g were used. They were housed in hanging wire cages and maintained as described above.

Surgery. Following their arrival in our laboratory, the animals were allowed a minimum of 1 week to habituate to their environment prior to surgery. For surgery, the rats were anaesthetized with sodium pentobarbital (Nembutal, 40–50 mg/kg, IP), placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) and implanted bilaterally with stainless steel guide cannulae (22 gauge) aimed at the corpus striatum. The dorsal surface of the cranium was made horizontal, and bregma and the skull surface were used as zero reference points. The coordinates for implantation were AP $+0.11$ cm, L ± 0.2 cm, V -0.55 cm chosen with reference to the atlas of Konig and Klippel (1963). The cannulae were secured to the skull using three stainless steel screws and dental acrylic. The skin was sutured around the guide cannulae and the animals were returned to their home cages for a minimum 1-week recovery period, during which time they were handled daily.

Apparatus. The test apparatus has previously been described in detail (Dourish et al. 1983). Briefly, testing was conducted in four individual Perspex cages (40 cm square, 23 cm high) positioned in automatic activity recording devices (Opto-Varimex Minor, equipped with option VS, Columbus Instruments, Columbus, OH, USA). A logic circuit in these devices enabled a distinction to be made between whole-body ambulatory movements and photobeam interruptions due to other movements made by the animals. Total horizontal activity (including grooming, scratching, head swaying, tail movements, etc.) was determined by the interruption of any one of 12×12 infrared photobeams (3 cm apart) in any order. Ambulation (coordinated locomotion), on the other hand, was determined by the interruption of consecutive photobeams. Vertical activity (rearing and jumping) was measured by units equipped with a series of 12 photobeams (3 cm apart) which were suspended (15 cm above cage base) from the cage walls. Interruption of any photobeam produced a 1-ms pulse which was counted by a microprocessor/Apple II Computer System.

Procedure. In initial studies on the central effects of piribedil, animals were habituated to the test cages for 60 min prior to injection. In subsequent studies on apomorphine-induced yawning, animals were tested under novel conditions, since a sedative effect is more readily detected when animals exhibit high baseline activity levels. The injection assembly consisted of two 30-gauge internal cannulae (Plastic Products Co., Roanoke, VA, USA), each of which was connected by PE-10 tubing (Plastic Products Co.) to a 5-µl syringe (SGE, Melbourne, Australia). For injection, each rat was removed from the cage and the injection cannulae lowered into the brain tissue on both sides to a depth of 0.5 mm below the tips of the guide cannulae. The injections were administered manually over a period of 1–2 min. The cannulae were left in situ for an additional 30 s to allow for diffusion of the solution away from the tip of the injection cannulae. Fluid flow in the injection cannula was verified by noting the movement of a small air bubble in the PE tubing. The animal was then placed in the test cage for a 60-min test. Activity data were recorded automatically at 5-min intervals by the microcomputer and, in addition, an observer continuously observed the animals and recorded the frequency of occurrence of other behavioural responses during the same time intervals. The number of yawns was counted during each 5-min interval. Grooming, sniffing, and chewing were rated on a five-point scale during each 5-min interval (see legend to Table 2 for further details). A minimum of five animals were tested in each treatment condition (see Results for details).

Drugs. All drug solutions were prepared fresh daily. Piribedil monomethane sulphonate (Les Laboratories Servier, Paris, France) and apomorphine hydrochloride (Sigma Chemical Co., St Louis, MO, USA) were dissolved in distilled water. Haloperidol base (Janssen Pharmaceutica, Beerse, Belgium) was dissolved in a minimum quantity of glacial acetic acid and diluted 40–50 times with saline. Scopolamine hydrobromide (Abbott Laboratories, Montreal, Canada) was obtained as 0.4 mg/ml injection ampoules and diluted as required with saline. Piribedil and apomorphine were injected intracranially in a volume of 1 µl per cannula (except for 20 µg apomorphine, which was injected in a volume of 1.5 µl per cannula, due to insolubility at the lower volume). An equivalent volume of saline was administered as a control. All animals received drug (either piribedil or apomorphine but not both) and control treatments and the order of testing was varied between animals to avoid order effects. Each rat was given a maximum of four microinjections into brain tissue. Haloperidol (or vehicle) was injected IP 30 min prior to intrastriatal piribedil and scopolamine (or vehicle) was injected IP 30 min after intrastriatal piribedil. Systemic piribedil and apomorphine injections were administered SC in the flank in a volume of 1 ml/kg. Drug doses are expressed in terms of the salt (piribedil, apomorphine, scopolamine) or the base (haloperidol).

Statistical analysis. Normally distributed parametric data were analysed by analysis of variance (ANOVA). Where ANOVA yielded a significant result, individual group differences were determined by appropriate *t*-tests. Non-normally distributed parametric data and non-parametric data

were analysed by Wilcoxon test (correlated samples) or by Mann-Whitney U test (independent samples). A probability level of $P<0.05$ was regarded as significant.

Histology. At the end of the experimental schedule the animals were sacrificed and their brains removed and fixed in formaldehyde (20% v/v) for at least 12 h. Subsequently, the brains were sectioned at 60 μm on a freezing microtome and the slices mounted on glass slides and inspected microscopically. The positions of the tips of the cannulae were verified according to the atlas of Konig and Klippel (1963). Only animals in which injection cannulae tracks entered the corpus striatum were used in the analysis of results.

Results

1. Systemic injections

Table 1 shows the effects of SC injection of piribedil and apomorphine on yawning, penile grooming, and chewing. Both piribedil ($F_{2,15}=4.63$, $P<0.05$) and apomorphine ($F_{2,27}=8.26$, $P<0.01$) significantly increased yawning. The effects were dose related and 2.5 mg/kg piribedil and 0.1 mg/kg apomorphine elicited peak increases in the response. Higher doses of either drug (i.e., 5–10 mg/kg piribedil, 0.5–1.0 mg/kg apomorphine) increased sniffing but did not increase yawning (data not shown).

The time course of piribedil-induced yawning is illustrated in Fig. 1. Yawning appeared 10–18 min after injection and disappeared 40–50 min after drug treatment. Apomorphine-induced yawning appeared 5–10 min after injection and disappeared 30–40 min after drug treatment. Yawning, elicited by SC apomorphine and piribedil, was associated with increased chewing mouth movements (Table 1). Generally, yawning was both preceded and succeeded by chewing and there was a significant correlation between the two responses in drug-treated rats (Spearman's $r=0.69$, $P<0.01$). In addition, piribedil and apomorphine tended to increase penile grooming although ANOVA revealed that these effects were not significant, presumably due to large within group variance. Both drugs produced occasional stretching associated with yawning but this response was too infrequent to merit quantitative assessment.

Table 1. Effects of piribedil and apomorphine on yawning, penile grooming, and chewing following SC injection in male rats

Treatment	n	Yawning	Penile grooming	Chewing
Saline	6	0.2±0.2	0.3±0.2	6.5± 2.9
Piribedil 1.25 mg/kg	6	13.6±5.5*	1.8±0.7	16.3± 7.2
Piribedil 2.5 mg/kg	6	18.2±5.1**	2.5±0.8	47.7±10.3*
Apomorphine 0.1 mg/kg	20	17.5±2.1***	2.9±0.7	25.9± 4.0*
Apomorphine 0.2 mg/kg	4	11.2±7.2	5.0±2.1	18.5±12.0

Data are expressed as mean (±SE) number of episodes during a 60-min test. Significant differences were determined by two tailed t-test for independent means following a significant ANOVA result.

* $P<0.05$; ** $P<0.01$; *** $P<0.001$

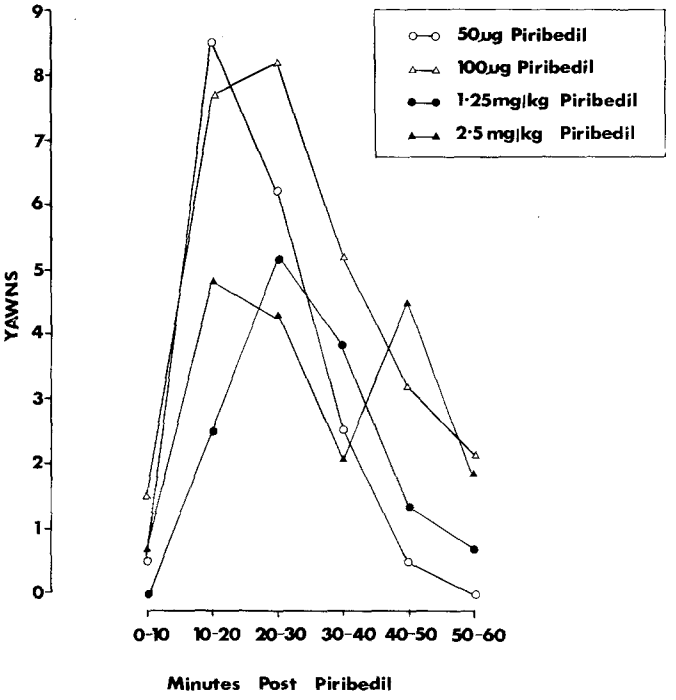

Fig. 1. Time course of yawning elicited by piribedil microinjected bilaterally into the striatum or systemically injected SC. Doses are expressed as micrograms bilaterally or milligrams per kilogram. Data are mean number of yawns per 10 min (SE omitted for clarity)

2. Central injections

Histology. The data are based on 18 subjects (13 treated with piribedil and 5 treated with apomorphine) with bilateral cannulae placements located in the striatum. Bilateral injection sites for each subject are displayed in Fig. 2. It is apparent from Fig. 2 that the majority of injection sites were located close together in the ventromedial striatum. The behavioural effects described below were obtained in all animals which had striatal placements. In 15 animals tested with cannulae placements outside the striatum and located in various adjacent brain sites (e.g., olfactory tract, cortex, insulae calleja, fascilus medialis prosencephali, anterior commisure) injection of dopamine agonists failed to elicit yawning.

Effects of intrastriatal piribedil on yawning. The effect of piribedil on yawning following local microinjection into the striatum of male rats is shown in Table 2. Piribedil elicited a significant increase in yawning, an observation which was confirmed by ANOVA ($F_{5,47}=15.14$, $P<0.01$). The response was dose dependent, and 100 μg piribedil elicited a higher frequency of yawning than 50 μg piribedil ($P<0.05$, correlated t-test).

The time course of the yawning response elicited by intrastriatal piribedil is illustrated in Fig. 1. Yawning appeared 7–8 min after injection, was maximal from 15 to 35 min and declined thereafter. Little or no yawning was evident at the end of the 1-h test period.

IP injection of 1 mg/kg scopolamine 30 min after intrastriatal application of 100 μg piribedil (when the yawning response was maximal) abolished yawning (Fig. 3). After scopolamine injection, piribedil-treated animals became active and exhibited locomotion, sniffing and exploration of

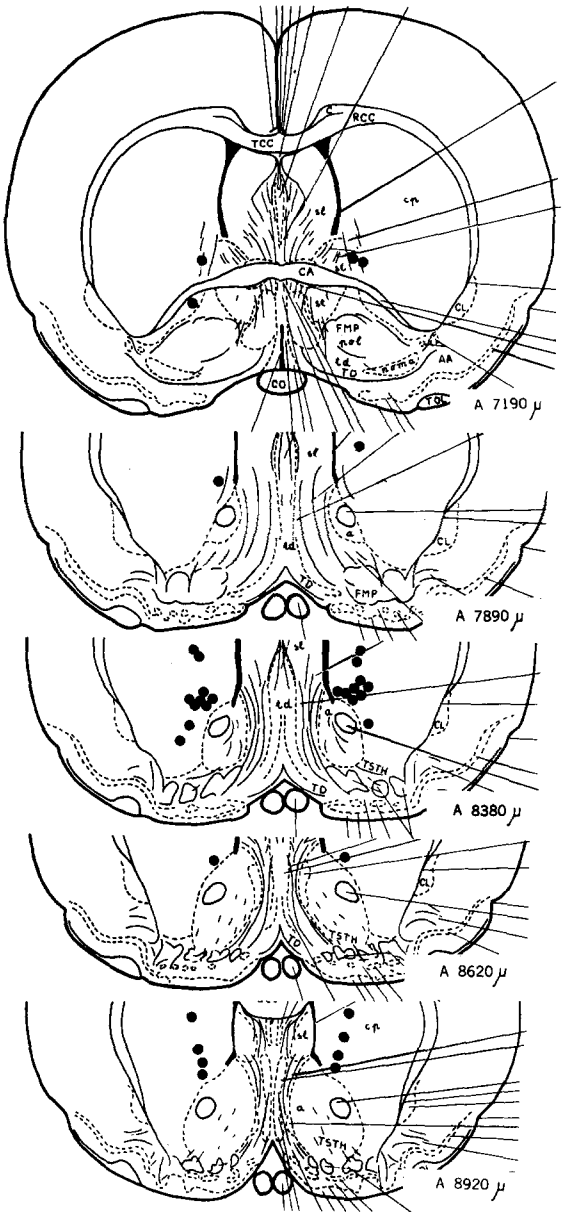

Fig. 2. Composite diagram showing bilateral injection sites located within the corpus striatum. Injection sites are represented by filled circles. Sections are according to the atlas of Konig and Klippel (1963)

the test cage (see also Fig. 5). Similarly, IP injection of 25 μg/kg haloperidol, 30 min prior to intrastriatal application of 100 μg piribedil, antagonized the yawning response (Fig. 4).

Effects of intrastriatal piribedil on stretching, grooming, sniffing, and chewing. Piribedil-induced yawning was accompanied by chewing, penilegrooming and occasional stretching. Quantitative assessment of stretching was not carried out. However, qualitative observation revealed that stretching was confined to the forelimbs and was generally co-ordinated with yawning. The elicited-stretching could involve either one or both forelimbs but did not involve the hindlimbs or hindtrunk region. When penile grooming occurred, this response was generally vigorous and was often accompanied by erection and ejaculation. Interestingly,

Table 2. Effects of piribedil on yawning, chewing, sniffing, and grooming following bilateral microinjection into the corpus striatum of male rats

Treatment	*n*	Yawning	Grooming	Sniffing	Chewing
Saline	13	2.3±1.4	4	26.5	0
Piribedil 50 μg	5	16.8±5.7**	11	28	19*
Piribedil 100 μg	13	27.6±3.2**	9	25	16*

Yawns are expressed as mean±SE for a 1-h test. Significant differences were determined by two-tailed *t*-test for correlated means after a significant ANOVA result. Grooming, sniffing and chewing were rated on a five-point scale at 5-min intervals for 1 h (0=absent; 1=mild intensity; 2=moderate intensity; 3=high intensity; 4=severe; maximum score 12×4=48). Values in the table are median scores. Significant differences were determined by Wilcoxon test

* $P<0.01$; ** $P<0.005$

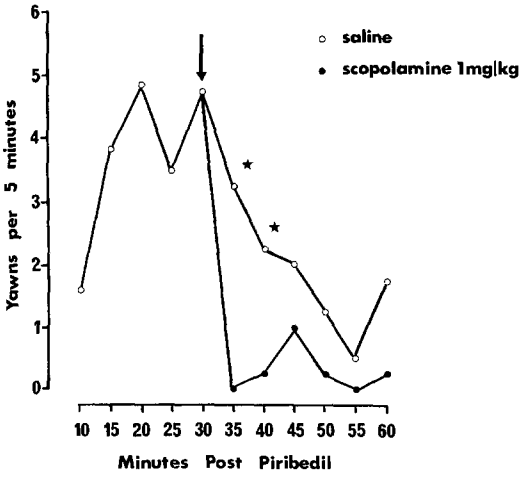

Fig. 3. Blockade by IP scopolamine of yawning elicited by intrastriatal injection of 100 μg piribedil ($n=4$). Data are mean number of yawns per 5 min. Scopolamine (or vehicle) was injected 30 min after piribedil (indicated by ↓). Significant differences between drug and Saline pretreatments were determined by *t*-test for correlated means: $\star P<0.05$

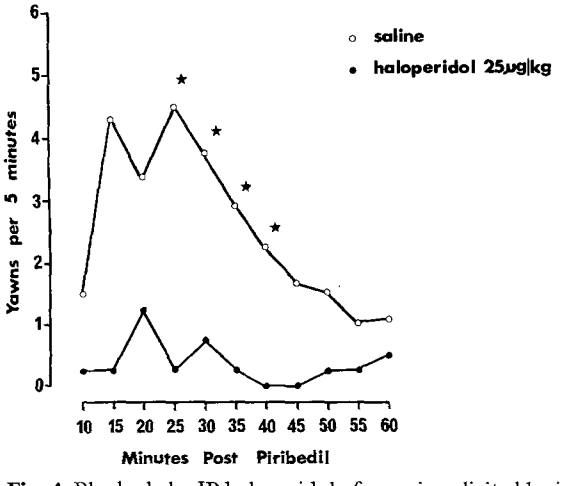

Fig. 4. Blockade by IP haloperidol of yawning elicited by intrastriatal injection of 100μg piribedil ($n=4$). Haloperidol (or vehicle) was injected 30 min before piribedil. Other details are as in Fig. 3

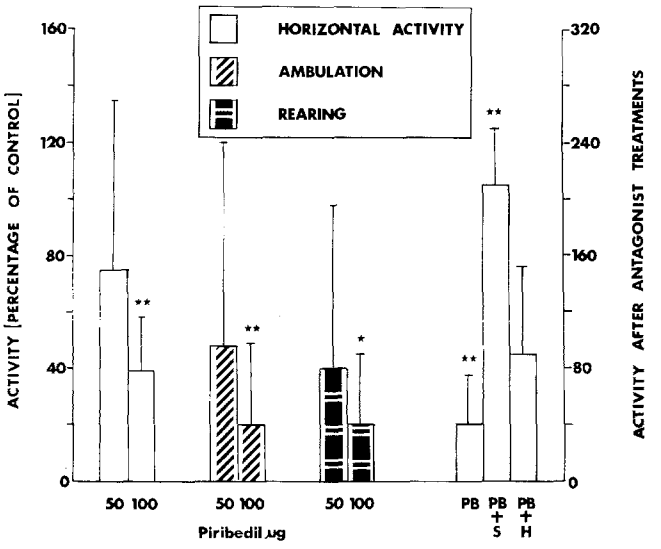

Fig. 5. In the left portion of the graph the effects of 50 µg piribedil ($n=5$) and 100 µg piribedil ($n=13$) applied bilaterally to the striatum on horizontal activity, ambulation, and rearing are shown. Data for piribedil treatment are expressed as mean ± SE percentage of saline scores ($n=13$). On the right portion of the graph the effects of systemic injection of haloperidol (H) and scopolamine (S) on piribedil-induced decrements in horizontal activity are shown. Significant differences between drug and control treatments were determined by Wilcoxon test: $^{*}P<0.05$, $^{**}P<0.01$

there appeared to be a relationship between the occurrence of penile grooming and the frequency of the yawning response. Thus, animals which showed penile grooming also exhibited a very high frequency of yawning. Although penile grooming was scored under the general category of grooming (Table 2), statistical analysis of penile grooming as a separate category failed to reveal any significant between-group differences, due to large within-group variation in response to piribedil. Piribedil-induced yawning was generally preceded and succeeded by chewing movements of the jaws, which were also associated with yawning produced by systemic piribedil (see Table 1). There was a highly significant correlation between yawning and chewing induced by intracranial piribedil application ($r=0.77$, $P<0.002$).

Effects of intrastriatal piribedil on photocell activity measures. The effects of piribedil on photocell activity measures, expressed as percentage of control values, are displayed in Fig. 5. Piribedil tended to decrease total horizontal activity at both doses. However, due to large within-group variation, only the 100 µg drug treatment produced a significant decrease in total horizontal activity. Similarly, 100 µg piribedil elicited a significant decrease in ambulation and in rearing (Fig. 5).

The depressant effect on horizontal activity of 100 µg piribedil injected into the striatum was abolished by pretreatment with 25 µg/kg haloperidol given IP (Fig. 5). Similarly, IP injection of 1 mg/kg scopolamine 30 min after intrastriatal application of 100 µg piribedil reversed the locomotor depressant effect of piribedil into a significant increase in total horizontal activity scores (Fig. 5). Scopolamine and haloperidol treatment also antagonized the decrease in ambulation and rearing produced by 100 µg piribedil applied to the striatum (data not shown).

Table 3. Effects of apomorphine on yawning, chewing, sniffing, and grooming following bilateral microinjection into the corpus striatum of male rats

Treatment	Yawning	Grooming	Sniffing	Chewing
Saline	2.2 ± 1.3	17	36	5
Apomorphine 5 µg	16.5 ± 9.4	11*	20*	21*
Apomorphine 10 µg	12.2 ± 4.0**	12	24*	23*
Apomorphine 20 µg	16.0 ± 7.8*	5	28*	25*

Yawns are expressed as mean ± SE for five rats. Significant differences were determined by two-tailed *t*-test for correlated means following a significant ANOVA result. Other behaviours are median scores for five rats on the scale described in Table 2. Significant differences were determined by Wilcoxon test

* $P<0.05$; ** $P<0.025$

Table 4. Effects of apomorphine microinjected bilaterally into the corpus striatum on photocell measures of activity

Treatment	Total horizontal activity	Ambulation	Vertical activity
Saline	3,254 ± 532	1,027 ± 423	61.6 ± 17.2
Apomorphine 5 µg	1,474 ± 243	648 ± 99	15.6 ± 4.2*
Apomorphine 10 µg	2,772 ± 1,418	1,382 ± 903	30.4 ± 17.2
Apomorphine 20 µg	2.610 ± 741	1,131 ± 325	13.6 ± 4.8*

Values are mean ± SE of five rats. Statistical comparisons between drug and control treatments were made by *t*-test for correlated means following a significant ANOVA result: * $P<0.025$

Effects of intrastriatal apomorphine on yawning, grooming, sniffing, and chewing. The dose-response effects of intrastriatal application of apomorphine on yawning are shown in Table 3. Apomorphine at doses of 10 and 20 µg elicited significant increases in yawning. Yawning induced by intracerebral apomorphine was identical to that induced by SC injection of the drug and was accompanied by chewing, penile grooming and stretching. Yawning appeared 4–10 min after injection and disappeared 40–50 min after drug treatment. A dose of 5 µg apomorphine significantly decreased grooming in a novel environment (Table 3). The drug effect at the 20 µg dose, however, was variable, since three rats showed little or no grooming whereas two animals engaged in long periods of penile grooming (accompanied by erection and ejaculation) and, therefore, attained high scores on the rating system used. Apomorphine-induced penile grooming was associated with a high frequency of yawning, as observed with the piribedil response. Consistent within-group effects were observed on chewing, which was increased by intrastriatal apomorphine in a dose-dependent manner (Table 3). Chewing induced by central apomorphine generally preceded and succeeded yawning as observed after systemic drug treatment. Sniffing in a novel environment was decreased by all doses of intrastriatal apomorphine (Table 3).

Effects of intrastriatal apomorphine on photocell activity measures. There were no differences in total horizontal activity or ambulation between any of the treatment groups (Table 4). However, ANOVA revealed a significant effect of apomorphine on vertical activity ($F_{3,15}=3.49$, $P<0.05$).

Table 5. Comparative effects of intrastriatal and systemic injections of dopamine agonists on yawning in rats

Treatment	Mean number of yawns (1 h)	Mean latency to onset (min)	Maximum duration (min)
SC Piribedil	16	14	35
IS Piribedil	22	7.5	50
SC Apomorphine	14	8	20
IS Apomorphine	15	5	40

All the above treatments produced an identical syndrome of yawning and chewing accompanied by intermittent sexual arousal (penile grooming, erection and ejaculation) and stretching. SC = subcutaneous; IS = intrastriatal; data were combined across doses to generate overall mean scores for latency, duration and frequency of yawning

Further analysis by correlated *t*-test indicated that 5 and 20 µg apomorphine significantly decreased vertical activity (Table 4).

Discussion

Local bilateral application of piribedil and apomorphine to the striatum of male rats produced yawning which was both preceded and succeeded by chewing mouth movements. On some occasions, yawning was accompanied by sexual arousal (penile grooming, erection and ejaculation) and forelimb stretching. Both piribedil and apomorphine are direct dopamine receptor agonists (for reviews see Dourish 1983; DiChiara and Gessa 1978), and it therefore seems likely that yawning was produced by dopamine receptor stimulation.

The yawning syndrome produced by central application of piribedil and apomorphine was compared with that elicited by systemic administration of small doses of the same drugs (see Table 5). Both routes of injection produced dose-related yawning and chewing with intermittent penile grooming and stretching. These results confirm that yawning is produced by systemic administration of low doses of dopamine agonists (Mogilnicka and Klimek 1977; Protais et al. 1983; Baggio and Ferrari 1983). In the present study, peak effects on yawning were produced by SC doses of 0.1 mg/kg apomorphine and 2.5 mg/kg piribedil, which is consistent with previous studies on the dose-response effects of dopamine agonists on yawning (Protais et al. 1983; Yamada and Furukawa 1980). In addition, our results indicate that the response involves brain dopamine receptors since yawning is produced by intracerebral application of piribedil and apomorphine. Generally, the syndrome induced by intrastriatal piribedil had a shorter latency to onset and a longer duration than that produced by systemic injection of the drug, which suggests that the response is centrally mediated (Table 5). Indeed, it seems implausible that the response could be due to stimulation of peripheral dopamine receptors, since it has recently been reported that the peripheral dopamine antagonist domperidone does not inhibit yawning induced by systemic apomorphine (Stahle and Ungerstedt 1984). In contrast, central dopamine receptor blockade by haloperidol abolishes yawning induced by systemic or intracerebral dopamine agonists (Protais et al. 1983, present data).

Interestingly, only one previous study (Yamada and Furukawa 1980) has noted that yawning elicited by SC piribedil is associated with increased chewing mouth movements. The present data convincingly demonstrate that there is a sigificant correlation between yawning and chewing produced by both systemic and intracranial administration of dopamine agonists. Therefore, we believe that chewing is an integral part of the yawning response in rats. Furthermore, haloperidol pretreatment or bilateral 6-hydroxydopamine (6-OHDA) lesions of the striatum abolish yawning and chewing induced by dopamine agonists (Dourish et al. 1985; Dourish and Cooper unpublished results).

Yawning induced by systemic dopamine agonist injection is thought to be the consequence of an inhibition of dopaminergic transmission mediated by the stimulation of dopamine autoreceptors in the brain (Serra et al. 1983a, b; Protais et al. 1983; Yamada and Furukawa 1980; Baggio and Ferrari 1983). Thus, doses of dopamine agonists which induce yawning after systemic injection are within the range thought to activate autoreceptors, but lower than doses required to produce signs of postsynaptic dopamine receptor stimulation such as hyperactivity and stereotypy (Serra et al. 1983a, b; Stahle and Ungerstedt 1984; Baggio and Ferrari 1983). Furthermore, two recently synthesized drugs, TL-99 and (+) 3-PPP which have been claimed to have a selective agonistic action at dopamine autoreceptors (Hjorth et al. 1981; Goodale et al. 1980) induce yawning in rats (Mogilnicka et al. 1984; Stahle and Ungerstedt 1984). In addition, 6-OHDA lesions of the striatum abolish yawning induced by systemic apomorphine injection (Dourish et al. 1985), indicating that the dopamine receptors involved in the production of the response are probably located pre-synaptically.

Considerable interest is now developing in dopamine agonist-induced yawning (cf. Serra et al. 1983a, b; Protais et al. 1983; Mogilnicka et al. 1984; Stahle and Ungerstedt 1984), and the suggestion has been made that it can be used as a behavioural index of central dopamine autoreceptor stimulation (Stahle and Ungerstedt 1984; Gower et al. 1984). This suggestion is fully consistent with the evidence available from systemic drug administration studies and it is difficult to conceive of an alternative explanation of these data. The present data show that an identical yawning syndrome can be elicited by direct injection of dopamine agonists into the striatum. The most parsimonious explanation of these data is that yawning induced by central dopamine agonist injection is also autoreceptor mediated, particularly in view of the observation that a very low dose of haloperidol abolished yawning elicited by intrastriatal piribedil. However, this interpretation is speculative and the possibility of postsynaptic dopamine receptor mediation of the syndrome elicited by intracerebral application of piribedil and apomorphine cannot be ruled out because of the relatively large drug doses which were applied to the striatum to produce yawning. Further studies, incorporating central application of the putative autoreceptor agonists 3-PPP and TL-99 and the putative autoreceptor antagonist sulpiride are necessary to directly test the dopamine autoreceptor hypothesis. In addition, in vivo studies of striatal dopamine metabolism after dopamine agonist treatment using brain dialysis (Hutson et al. 1985) may prove extremely valuable in the investigation of dopaminergic involvement in yawning.

The muscarinic antagonist scopolamine inhibited yawn-

ing elicited by intrastriatal piribedil and therefore it appears that there is some cholinergic involvement in yawning. It has been claimed that yawning may be a consequence of the release of cholinergic neurones from inhibition by dopaminergic neurones (Yamada and Furukawa 1980; Urba-Holmgren et al. 1980). The present data are compatible with such a proposal. However, this hypothesis was not tested directly and further studies of the effects of central application of cholinergic agonists and antagonists (e.g., carbachol, scopolamine) should provide important information on the neural substrates of yawning.

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