Is there a chance of bridging the gap between the cellular and the computational level?

It is certainly true that behavioral experiments may provide us with an opportunity to determine successfully the particular neuronal implementation of computational operations within the nervous system [3]. But we know that the more we deviate from the primary sensory neuron, or from the motoneuron via a chain of interneurons to the brain, the more difficult it is to explore how the proper stimulus is encoded and a motor pattern performed. As shown by Schildberger (this issue), some local auditory neurons within the cricket brain act as elements intimately related to conspecific song recognition. When compared with primary sensory and ascending auditory neurons they lose both intensity dependence and synchronization of their activity to phonotactically essential temporal parameters. What is the neural parameter for which we have to look, and what does it tell us about the computation used? Even though we may end up with a set of neurons called 'complex feature detectors' solely responding to distinct stimulus configurations, our task is not at an end; it is just beginning.

As Heiligenberg [3] has pointed out so rightly, one may indeed wonder whether a coherent theory of brain and behavior can ultimately be formulated, even for invertebrates, at the level of individual neuronal activities. It may well turn out that we face some kind of higher-level language, detached from single neurons, as the only possible solution. It is my strong feeling that the relationship between neuronal implementation and the computational level will not be found soon, and that this gap is perhaps the strongest challenge for neuroethology in the future.

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Full Papers

Pharmacodynamic profile of CQP 201-403, a novel 8α-amino-ergoline*

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Summary. The profile of action in animals of CQP 201-403, a novel 8α-amino-ergoline, is in most aspects that of a very potent dopaminomimetic, both as a prolactin secretion inhibitor, and at the levels of the CNS and the cardiovascular system. Qualitatively CQP 201-403 differs slightly from bromocriptine and apomorphine in its effects on the CNS (no influence on serotonin metabolism in the rat cortex; induction of masculine mounting behavior in rats) and the cardiovascular system of the dog (reflex tachycardia in response to a blood-pressure fall). In man the new compound proved to be highly active in lowering prolactin serum levels and to be more potent than bromocriptine (Parlodel®).
Key words. CQP 201-403; 8α-amino-ergolines; ergot pharmacology; D-2 agonist; endocrine; CNS; cardiovascular actions.

Introduction

Twenty years ago 2-Br-α-ergocryptine mesylate, an ergopeptine, was reported to inhibit prolactin secretion in the rat [1]. It became the first drug to be selected and developed for this property (CB 154, bromocriptine, Parlodel®, Pravidel®). The interest which bromocriptine aroused motivated numerous attempts to make further improvements. With other ergopeptines this failed, but ergolines, especially 8α-amino-ergolines, seemed more promising. Compounds CH-29-717 [2], CQ 32-084 and CU 32-085, mesulergine [3] were the results of such attempts, and CQP 201-403 is the latest compound in this line. Figure 1 shows the chemical structure of CQP 201-403 and the two related compounds used in this study.

Materials

CQP 201-403 is the Sandoz code number for the hydrochloride of N,N-Diethyl-N′-(6-propylergoline-8α-yl) sulfamide, relative mol. wt 440.5. It was synthesized from the corresponding carbobenzoxy protected 8α-amino-ergoline derivative by N(6)-demethylation followed by N(6)-propylation. After deprotection, the 8α-amino group was reacted with diethylsulfamoylchloride to give the free base of CQP 201-403 [4]. CQP 201-403 and related compounds used in this study were used dissolved in acidified ethanol and diluted with physiological saline. CQ 32-084 and CH 29-717 were used as the hydrochlorides, while bromocriptine (formula not shown) was used as the mesylate (rel. mol. wt 751). In a few experiments, pergolide [5], apomorphine or α-ergocryptine were tested for comparison.

Methods

Effects on the control of pituitary hormone secretion

1) Lowering of basal prolactin serum levels in male rats: Groups of male rats (SIV 50) were used as described earlier [2] to determine by RIA the doses of test drugs lowering serum prolactin levels by 50% (ID50) at different times after s.c. treatment.

2) Prolactin suppression assessed by implantation (nidation) inhibition in progravid rats: As described earlier in detail [2, 3], groups of progravid rats were treated on day 5 after insemination and autopsied on day 12 for inspection of uteri for nidation sites. Doses of drugs were determined which lowered implantation rate by 50% (ED50). These values were calculated from the various dose groups by the probit method.

3) Lactation inhibition in rats; a model for assessing suppression of stimulated prolatin secretion: As decribed earlier [2, 3], groups of lactating rats were treated orally for 4 days with test drugs using several doses. The pup body weight development was assessed daily during pre- and postreatment days as a measure of milk yield of the dams. ID50 values were calculated from the weight gain curves of the pups.

4) Inhibition of milk ejection in rats as indicator of suppressed reflex oxytocin release: The experiments were performed as described by Grosvenor and Turner [6]. Briefly, lactating dams were separated from their pups for 8 h. Three hours after separation, 2 groups of dams (A,B) were treated with the drug and 1 group (C) with solvent. At 7¾ h after separation dams of drug group B received oxytocin s.c. (0.5 I.U.), and groups A and C physiological saline. Just before returning the pups to their dams they were weighed. Fifteen minutes after nursing had begun, oxytocin was given as before to group B. Fifteen minutes later the pups were weighed once more. The weight gains of the three groups were compared. Doses used were multiples of ED50 for implantation inhibition.

Methods for assessing central actions

5) Observation of behavioral changes in freely moving rats: Male Wistar rats were observed for drug-induced behavioral changes. The method of observation was a modified form of that described by Irwin [7]. In short, the rats were placed in groups of 3 in macrolon cages and their behavior observed for 2½ h continuously and if necessary for a further 4 h at ½-h intervals. Spontaneous activity, reactivity, behavioral abnormalities such as stereotyped movements, possible neurological disturbances, vegetative side effects including changes in deep-rectal temperature, were assessed using a multi-parametric check list.

6) Rotational movements in 'Ungerstedt' rats: Unilateral lesions of the substantia nigra (SN) in male rats (OFA, 150–160 g) were produced by microinjection of 6-OH DA as described by Ungerstedt and Arbuthnott [8, 9]. Rotational movements induced by drugs were recorded using an automated rotameter.

7) Effects on locomotion in mice (NMRI strain): Locomotion was assessed automatically every 15 min for 7 h in a

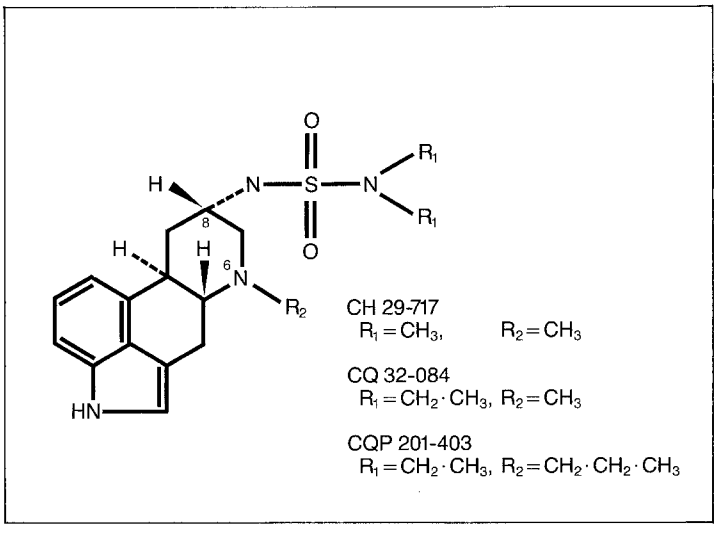

Figure 1. Chemical structure of the ergoline CQP 201-403 and two related compounds, CQ 32-084 and CH 29-717.

Motron cage. Groups of 5 naive mice were given the drug or vehicle s.c. immediately before introduction into the cage [9].
8) Emetic action in dogs: Groups of mongrel dogs (males and females, fasted overnight), were given in i.v. doses of the test drug 0.5 ml/kg injected over 60 s. Latency and frequency of vomiting were noted after different doses. Each dog was used only once a week. ED50 values were read from log-probit graphs.
9) Influence on monoamines and their metabolites in the rat brain: Male rats (OFA) (200–250 g) were used for these experiments. Animals were sacrificed by cervical dislocation at chosen intervals after oral administration of the test drug. Treatment of the animals was so scheduled as to permit sacrifice of all animals at noon, to exclude circadian changes in metabolism. The brain was immediately dissected according to the method of Glowinski and Iversen [10], frozen on dry ice and stored at −80 °C until analyzed. Dopamine and its metabolites in the striatum and cortex, noradrenaline and its metabolites in the pons/medulla and serotonin with its metabolites in the cortex were determined by GC/MS techniques as previously described [11–13]. In order to test ex vivo whether CQP 201-403 had presynaptic dopaminomimetic activity, 11.1 mg/kg of the compound was given orally to rats treated also with gamma-butyrolactone (GBL, 750 mg/kg i.p.) to induce DOPA accumulation, and m-hydroybenzylhydrazine (NSD, 100 mg/kg i.p.) to block decarboxylase activity [14].

Binding sites and receptor interactions
10) Inhibition of specific radioligand binding to CNS membranes: Ligand binding studies were performed in rat brain and calf caudate as described by Closse et al. [15].
11) Biochemical studies on dopamine receptor interactions: Studies were performed on D-2 controlled acetylcholine release from rat striatum slices from reserpinized rats and on D-1 controlled adenylate cyclase activity using bovine retinae, as described by Markstein et al. [16].

Method for assessing cardiovascular actions
12) The anesthetised dog: Mongrel dogs were used under chloralose (0.1 g/kg i.v.) and urethane (1 g/kg i.v.) anesthesia [17]. The effects of drugs on blood pressure and heart rate were examined. Each animal was given a single dose of drug as a bolus i.v. injection.

Results

Endocrine actions
1) Lowering of basal prolactin serum levels in male rats: The doses of CQP 201-403 required to lower basal serum prolactin levels by 50% (ID50) showed pronounced time dependence as seen in table 1. A comparison of these data with those from CB 154 experiments show that CQP 201-403 is severalfold more potent than the standard but with both drugs there was about a hundredfold increase in the ID50 values from 2 h to 24 h pretreatment time. A similar increase of ID50 values with time was also observed with pergolide.
2) Prolactin suppression assessed by implantation inhibition in pregravid rats: The ED50 of CQP 201-403 for ovum implantation inhibition, as observed on day 12 after insemination, was about 100 times lower than that of bromocriptine (table 2). CQ 32-084 was 4 times less potent, while the ED50 for CH 29-717 was about twice that of the new compound.
3) Lactation inhibition in rats; a model for assessing suppression of stimulated prolactin secretion: The development of body weight of pups nursed by actively treated dams was dose-dependently attenuated. As shown in table 3 the ID50 for CQP 201-403 was about 0.01 mg/kg orally (given for 4 days). The compound was clearly more potent than its congeners CQ 32-084 or CH 29-717. Bromocriptine given orally to rats was very weakly active.
4) Inhibition of milk-ejection in rats as an indication of suppressed reflex oxytocin release: As shown in table 4, a dose of CQP 201-403 4 times higher than the s.c. implantation-inhibitory ED50 value, and 3 times higher than the oral ID50 for lactation inhibition, did not reduce the amount of milk received in 30 min by hungry pups returned to their dam after a separation of 8 h. Similarly bromocriptine was also inactive, whereas α-ergocryptine inhibited the milk-ejection reflex. This effect was overcome by oxytocin.

Central actions
5) Observations on behavioral changes in freely moving rats: Minimal effective doses of CQP 201-403 and several other drugs are given in table 5. The ED50 for implantation inhibition is also shown for comparison.
The first central effect of CQP 201-403 was an increase in excitability which occurred with about the same dose as that necessary to suppress implantation. Activation of the rats and induction of sterotypies occurred at 10 times higher doses, while muscle tone, lid width and rectal temperature were reduced by doses 100 times higher. With pergolide, stereotypies occurred at the same doses as those at which excitability was increased, while lid width and rectal temperature were decreased at lower doses, i.e. at doses similar to those necessary to inhibit implantation. With bromocriptine, central effects were elicited with clearly lower doses than those necessary to inhibit implantation. With CQP 201-403, masculine mounting behavior occurred at high doses.

Table 1. Changes of ID50 values with time to suppress basal serum prolactin levels in male rats after s.c. treatment

Compound	ID50 µg/kg s.c.			
	2	4	8	24 h
CQP 201-403	0.33	1.3	1.6	38
CB 154	8	7	57	940
Pergolide 0.44	0.44	1.0	1.0	37

Table 2. ED50 mg/kg s.c. for the suppression of ovum nidation in the rat (treatment on day 5 after insemination)

Compound	ED 50 mg/kg s.c.
CQP 201-403	0.007
CQ 32-084	0.028
CH 29-717	0.012
CB 154	0.75

Table 3. ED50 mg/kg orally for 4 days to nursing rat dams, to inhibit pup weight gain (lactation inhibition)

Compound	ED50 mg/kg · d
CQP 201-403	0.01
CQ 32-084	0.130
CH 29-717	0.026
CB 154	6. (ca)

Table 4. Effect on milk-ejection reflex in lactating rats

Compound	Dose mg/kg s.c.	Effect
CQP 201-403	0.03	[a] None
CB 154	3.	[a] None
α-Ergokryptine	2.	[b] Suppression

Relative doses: [a] 4 × ED50 implant. inhibition; [b] 2 × ED50 implant. inhibition.

Table 5. Minimal effective doses (mg/kg s.c.) CQP 201-403 and other compounds to induce behavioral changes in freely moving rats

Compound	Activation	Stereotypies	Excitability increased	Mounting	Muscle tone	Lid width	Rectal temperature	Implantation↓
CQP 201-403	0.03	0.03	0.003	0.3	0.3↓	0.3↓	0.3↓	0.007
pergolide	0.1	0.03	0.03	∅	0.3↓↑	0.03↓	0.01↓	0.021
CB 154	0.3	0.3	0.3	∅	0.3↓	0.03↓	0.03↓	0.75

6) Rotational movements in 'Ungerstedt' rats: CQP 201-403, 0.01 mg/kg i.p., induced contralateral turning of maximally 6 rpm and a duration of 3–4 h. Pergolide was similarly active at this dose. After administration of 0.1 mg/kg i.p. the effect was stronger, and the duration of rotational movements was prolonged to 6–7 h.

7) Effects on locomotion in mice: CQP 201-403 stimulated locomotor activity in mice from a dose of 0.1 mg/kg s.c.. This effect was mainly seen during the 2nd to 7th h but it was also present during the first hour (the exploratory phase) following 0.3 mg/kg. Pergolide acted similarly.

8) Emetic action in dogs: CQP 201-403 induced vomiting in dogs with an ED50 of 0.7 ± 0.2 µg/kg i.v. For CB 154 the value was 7.5 µg/kg i.v.

9) Influence on monoamine metabolism in the rat brain: CQP 201-403 induced pronounced dose-dependent changes in the metabolism of monoamines.

Dopamine: HVA and DOPAC concentrations in the striatum were significantly reduced (20–30%) 2 h after 0.3 mg/kg orally. The DA concentration was significantly elevated from 10 mg/kg. Figure 2 shows that the biochemical effects in the striatum were fully developed 1 h after administration of 10 mg/kg, and were entrained for at least 6 h. In the cortex 10 mg/kg p.o. produced a significant reduction of HVA for 6 h. Figure 3 shows the evidence that CQP 201-403 has a presynaptic inhibitory effect on dopaminergic neurons in the striatum: CQP 201-403 inhibited the GBL-induced DOPA accumulation in the presence of decarboxylase blockade.

Noradrenaline: The concentrations in the hypothalamus and in the pons/medulla were significantly reduced 2 h after 10 mg/kg p.o., while MHGP sulfate was significantly and dose-dependently augmented in both tissues from 0.3 mg/kg orally to a maximum of about 200% of controls after 30 mg/kg. Figure 4 demonstrates that the changes of NA metabolism in the hypothalamus and pons/medulla after 10 mg/kg orally are significant after 1 h and maintained for at least 6 h.

Serotonin: Doses from 0.3 to 30 mg/kg orally did not induce significant changes in 5-HT or 6-HIAA concentrations in the rat cortex.

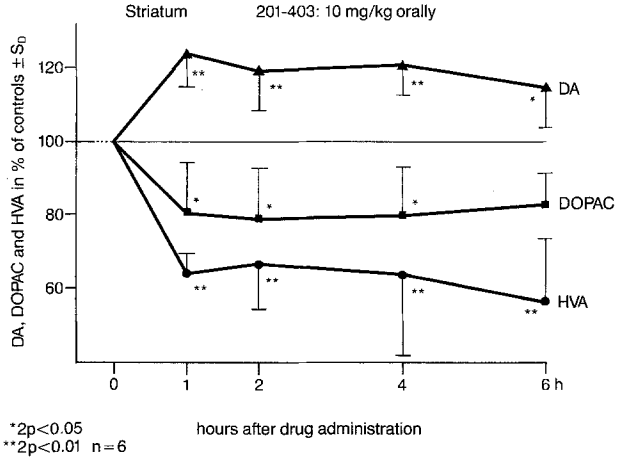

Figure 2. Changes in DA metabolism in the striatum of the rat at various time intervals after 10 mg/kg orally of CQP 201-403.

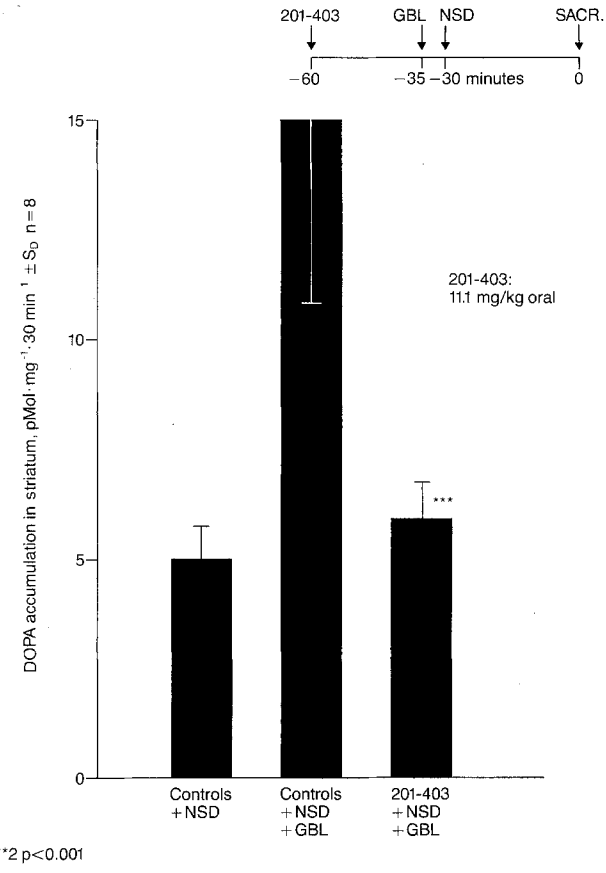

Figure 3. Effect of 11.1 mg/kg orally of CQP 201-403 on DOPA accumulation in the rat striatum after stimulation by gamma-butyrolactone (GBL, 750 mg/kg i.p.) and blockade of decarboxylase activity with m-hydroxybenzyl-hydrazine (NSD 1015, 100 mg/kg i.p.).

10) Inhibition of specific binding of radioligands to brain membranes: Table 6 gives IC 50 values for CQP 201-403 and related drugs for competing with [^{3}H]-ligand binding to membranes of brain tissue. It can be seen that the CQP 201-403 inhibitory activity on [^{3}H]-spiperone binding to frontal cortex membranes is similar to that on [^{3}H]-spiperone binding to calf caudate membranes. A relatively high activity is also seen at [^{3}H]-dopamine binding sites. CQ 32-084 had a similar profile of activity, while CH 29-717 showed a greater inhibition of [^{3}H]-spiperone binding to frontal cortex than to caudate membranes. Bromocriptine had maximum activity at SPC binding sites, but competitive activity at [^{3}H]-clonidine and [^{3}H]-WB 4101 α_2 and α_1 binding sites was of a similar magnitude.

11) Biochemical studies on dopamine receptor interactions: From table 7 it is clear that CQP 201-403 is an agonist at D-1 and D-2 receptors, like apomorphine. The D-1 activity lies in the micromolar range, while the D-2 activity occurs in the nanomolar range. CQP 201-403 is more potent at the D-2 receptor than bromocriptine or apomorphine.

12) Cardiovascular actions in anesthetised dogs: Intravenous administration of CQP 201-403 lowered blood pres-

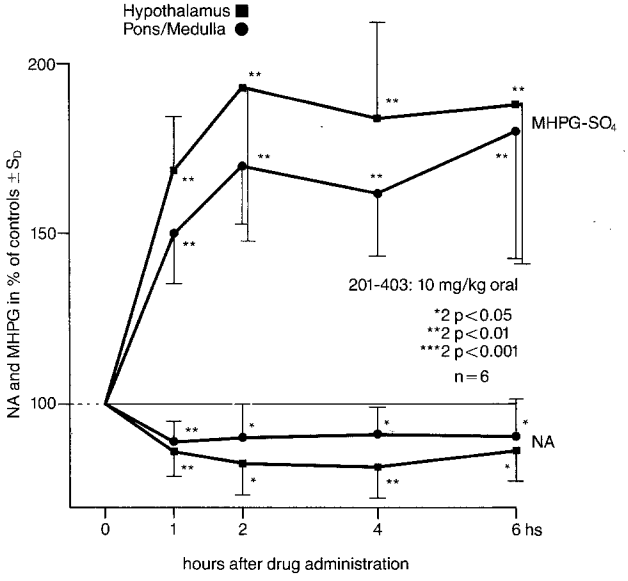

Figure 4. Changes in NA metabolism in the rat hypothalamus and pons/medulla at various time intervals after 10 mg/kg orally of CQP 201-403.

Table 6. Interactions with specific radioligand binding to membranes of rat and calf brain: IC50 (nM)

	5-HT	SPFC	Clon	WB4101	DA	SPC
CQP 201-403	170	22	1050	2600	99	6
CQ 32-084	5000	26	480	3300	120	25
CH 29-717	7000	40	320	5500	210	120
CB 154	225	76	29	33	84	13

Method as described by Closse et al.[14]. 5-HT = [^{3}H]-serotonin, whole rat brain, serotonin binding site; SPFC = [^{3}H]-spiperone, frontal cortex, serotonin binding sites; Clon = [^{3}H]-clonidine, rat brain without cerebellum, $\alpha 2$ binding sites; WB4101 = [^{3}H]-WB4101, whole rat brain, $\alpha 1$ binding sites; DA = [^{3}H]-dopamine, calf caudate, dopamine binding sites; SPC = [^{3}H]-spiperone, calf caudate, dopamine antagonist binding sites.

Table 7. Biochemical effects through D1 and D2 receptor stimulation

	D1 Adenylate cyclase stimulation bovine retina		D2 [^{3}H]-acetylcholine release inhibition rat striatum	
	E_r*	EC50 (μM)	%I	EC50 (nM)
CQP 201-403	49	2.0	79	0.4
Bromocriptine	∅		63	20.0
Apomorphine	44	0.6	86	25.0

E_r* = efficacy in % of maximal effect after 125 μM dopamine; %I = maximal inhibition in % of controls.

sure dose-dependently from 1.5 μg/kg. Hypotension was always associated with increases in heart rate which appeared to be related to the magnitude of the blood pressure fall. The response to 3 μg/kg lasted for more than 3 h. In experiments performed under the same experimental conditions, bromocriptine proved to be about 4 times less potent than CQP 201-403, but in contrast to the latter, rarely increased heart rate.

The hypotensive effect of CQP 201-403 3 μg/kg i.v. was completely abolished by pretreating the animals with 10 mg/kg i.v. sulpiride. Heart rate did not change significantly in these experiments, suggesting that the increases observed in the absence of sulpiride were reflex in nature.

Discussion

CQP 201-403 is a very potent inhibitor of basal or stimulated prolactin secretion in male and female rats. In in vitro cultures of rat pituitary cells and human prolactinoma cells, CQP 201-403 suppressed prolactin release in nanomolar concentrations and this effect persisted after wash-out[18]. In the implantation inhibition test, CQP 201-403, given s.c., was about 100 times more potent than bromocriptine, and a similar difference in potency by the oral route was observed in the lactation inhibition test. An investigation of the role of the alkyl substituents on the 8α-side chain (R1 in fig. 1) and on the N_6 substituent (R2 in fig. 1) was done in the (s.c.) implantation inhibition test and in the (oral) lactation inhibition test (table 8). Using homologues of CH 29-717[19] potency is increased equally with N_6-ethyl and with N_6-propyl. In the case of CQ 32-084, CQP 201-403 is the more potent of the two homologues. It was about 4 times more potent than CQ 32-084 by the s.c. route, and more than 10 time as potent by the oral route. In an N_6 homologue series studied with the ergopeptine bromocriptine, N_6-ethyl gave the highest potency[20] in inhibiting implantation.

The ID50 values for serum prolactin suppression by the s.c. route in male rats measured at 2, 4, 8 and 24 h after administration showed CQP 201-403 to be as active as pergolide and up to 30 times more active than bromocriptine. CQP showed about the same increase (100-fold) in the ID50 values during this period as did pergolide and bromocriptine, which implies a similar clearance for the three drugs. In studies in man, CQP 201-403 efficaciously lowered prolactin serum levels[21, 22], similar to pergolide[23].

The receptor mediating CQP 201-403-induced inhibition of prolactin has not yet been defined. From the non-endocrine profile of actions of the drug it may be deduced that prolactin secretion inhibition is effected by direct stimulation of dopamine receptors on the prolactin cells.

CQP 201-403, given acutely by the s.c. route, did not attenuate milk ejection in nursing rats, indicating that suckling-induced reflex oxytocin release is not blocked. The same is true for the related compounds CH 29-717 and CU 32-085[24] and for bromocriptine in this and an earlier study in the rat[25], and in the rabbit[26] where oxytocin was measured by RIA. A recent study[27], however, demonstrated an inhibitory dopaminergic regulation of oxytocin release in lactating rats, using bromocriptine. These contradictory observations cannot, at this time, be explained. Grosvenor described earlier that ergotamine blocked the milk-ejection reflex[28], and we observed α-ergokryptine and ergocornine[25] to inhibit milk ejection. This effect could be overcome by injecting the dams with oxytocin.

CQP 201-403 also affected various CNS and cardiovascular functions:

CQP 201-403 and pergolide induced locomotor activity in naive mice, and in contrast to bromocriptine and L-DOPA[9], did not attenuate locomotion during the exploratory phase

Table 8. Comparison in two tests in female rats of compounds structurally related to CQP 201-403

Substituents (see figure 1)		Clinical code number	ED50 Implantation inhib.	ID50 Lactation
R1	R2		mg/kg s.c.	
Me	Me	CH 29-717	0.013	0.03
Me	Et	–	0.002	ca. 0.003
Me	n-Propyl	–	0.002	ca. 0.003
Et	Me	CQ 32-084	0.028	0.13
Et	Et	–	0.011	ca. 0.02
Et	n-Propyl	CQP 201-403	0.007	ca. 0.01

Me = methyl, Et = ethyl.

(1st hour). Initial attenuation of locomotion is considered [29] to indicate presynaptic action, whereas stimulation of locomotion is thought to be due to postsynaptic receptor stimulation. Although these studies indicate that CQP 201-403 has no presynaptic dopaminomimetic activity, this conclusion is not supported by biochemical evidence (see below).

Behavioral effects seen in dogs (emesis) and rats were qualitatively similar to those of other dopaminominetic drugs like bromocriptine or pergolide. Quantitatively (table 5), these behavioral effects in the rat appeared at relatively higher doses (compared to the ED50 for implantation inhibition) after CQP 201-403 than after bromocriptine. One peculiar and unexpected effect distinguished the new drug from pergolide and bromocriptine: CQP 201-403 elicited at a high dose masculine mounting behavior. This effect had been observed earlier after administration of one other ergot derivative, lisuride [30, 31]. The mechanism underlying this behavior, which can be elicited in juvenile rats, adult female rats and gonadectomized rats, is not explained. Keller et al. [31] antagonized this effect with pimozide, a dopamine antagonist, or with 5-hydroxytryptophan, the precursor of 5-HT, and we prevented mounting after CQP 201-403 by pretreating rats with pimozide or a 5-HT receptor agonist, quipazine. A further study of drug effects on lisuride-induced mounting behavior in rats [32] demonstrated the possible involvement of opioid receptor mediated mechanisms. Morphine and the enkephalin analogue FK 33-824 [34] both inhibited lisuride-induced mounting, and this inhibition was reversed by naloxone. Thus a certain central dopamine stimulation and serotonin attenuation seems to be involved in producing this mounting behaviour which can be inhibited by opioid antagonists.

Biochemical evidence of central presynaptic dopamine receptor stimulation was clearly obtained (figs. 2, 3). Unexpectedly, in view of the mounting behavior observed, there were no changes in 5-HT metabolism in the rat cortex at doses up to 30 mg/kg. After apomorphine [34], brain serotonin metabolism is augmented, indicating increased serotoninergic activity. This is not in agreement with the evidence indicating that a serotoninergic deficit together with dopaminergic stimulation is at the base of masculine mounting behavior. It may be relevant, however, that serotonin metabolism was only measured in the cortex. Noradrenaline metabolism was increased, indicating an adrenoceptor blocking action of CQP 201-403.

CQP 201-403 lowered blood pressure in the anesthetized dog, an effect which was antagonized by sulpiride, indicating the dopaminomimetic nature of the effect. The reduction of the blood pressure in response to the compound was accompanied by reflex tachycardia, whereas after bromocriptine heart rate is rarely increased [17, 35, 36] and sometimes decreased [37], due to stimulation of prejunctional dopamine receptors on the accelerans nerve [38]. This finding suggests that CQP 201-403 does not have a significant effect on (pheripheral) accelerans nerve terminals, while in the brain there is good evidence for presynaptic dopaminomimetic stimulation (fig. 3).

In conclusion, CQP 201-403 is a very potent dopaminomimetic drug, clearly more potent than its parent compound CQ 32-084, especially by the oral route. CQP 201-403 differed qualitatively in certain aspects from bromocriptine, e.g. in only stimulating locomotion in mice and rat, in not affecting cortical serotonin metabolism, in inducing masculine mounting behavior in rats, and in permitting reflex tachycardia in response to a reduction in blood pressure.

* In memory of Dr Annemarie Closse, who died 14 June 1987.

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