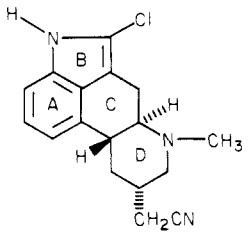
Communications to the Editor

Proposed Dopaminergic Pharmacophore of Lergotrile, Pergolide, and Related Ergot Alkaloid Derivatives

Sir:

The central dopamine agonist properties of certain derivatives of ergot alkaloids, typified by lergotrile (1) and



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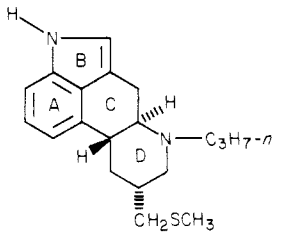

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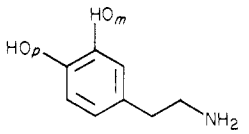

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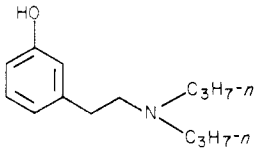
pergolide (2), have been well documented in the literature.[1,2] Marek and Roth[3] stated that 1 is a potent agonist at presynaptic dopamine receptors on striatal and mesolimbic nerve terminals. Goldstein et al.[4] concluded that lergotrile has the properties in the CNS of a mixed agonist–antagonist with respect to some presynaptic dopamine receptors. However, there seems to be little structural resemblance between 1 and 2 and dopamine (3), and a reviewer[5] stated in 1978 that ergot alkaloids bear little structural resemblance to the dopaminergic aporphines and 2-aminotetralins.

In 1978, one of us[6] suggested that lergotrile is related structurally to dopamine, if it is accepted that the weakly acidic indole NH group is bioisosteric with the "meta" OH of dopamine. The meta OH has been proposed[7] to be of considerable importance in agonist–receptor interaction. Some support is given to this proposal by the report of Geissler[8] that *N,N*-di-*n*-propyl-*m*-tyramine (4) has dop-



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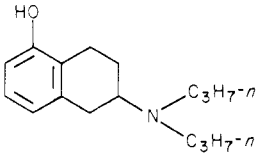

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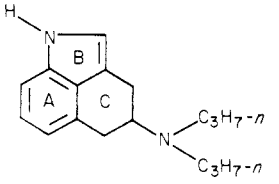
amine agonist actions and the report of McDermed et al.[9] that 2-(di-*n*-propylamino)-5-hydroxytetralin (5) is a potent dopaminergic. Bach and Kornfeld[10] described the ergoline fragment 6 and stated that it inhibited prolactin secretion



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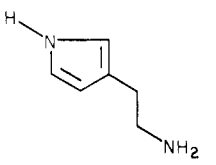

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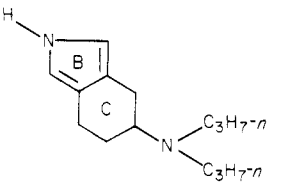

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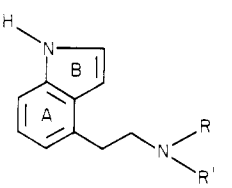

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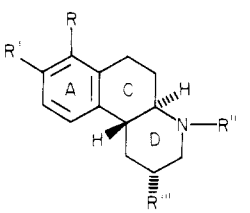

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and dopamine binding, which are characteristic actions of dopaminergic agonists. Bach et al.[11] found that 3-(2-aminoethyl)pyrrole (7) was ineffective in lowering prolactin levels, which was attributed to rapid metabolic inactivation of the primary amine by monoamine oxidase. No tertiary amine derivative of 7 was reported. Compound 8, a BC bicyclic ergoline partial structure, exhibited prolactin inhibitory activity, as well as some activity in a rat rotation assay, albeit in high doses in both assays. Bach et al.[12] have reported that depyrroloergolines (10, R = R′ = H; R″ = *n*-C_3H_7; R‴ = CH_2SCH_3) are dopaminergically inactive in two tests. In contrast, catechol derivatives of 10 (R = R′ = OH; R″ = alkyl; R‴ = H) are highly active, potent dopaminergics.[6]

Inspection of the molecular structures of lergotrile (1) and pergolide (2) suggested that the pharmacophore of lergotrile, pergolide, and 6 may be a 4-(2-aminoethyl)indole system, 9. Hofmann and Troxler[13] described derivatives of 9 (R, R′ = H, Me) and suggested that these "could be used in treatment of asthma". However, the literature has not revealed that they have been evaluated for dop-

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Table I. Sympathetic Neuronal Inhibiting Activity of Lergotrile (1), Pergolide (2), and 4-[2-(Di-n-Propylamino)ethyl]indole (9) in Anesthetized Cats

no.	dose, μg/kg	% inhibn of cardioaccelerator nerve stimulation, 2 Hz	inhibitory effect reversed by haloperidol, 100 μg/kg	ID_{50}, μmol/kg (95% CL)	potency ratio[a] rel to apomorphine (fiducial limits)
1	30	21 ± 7	yes, $p < 0.01$, $n = 5$	0.27 (0.13-0.62)	0.08 (0.04-0.16)
	100	57 ± 12			
	300	69 ± 10			
2	3	23 ± 3	yes, $p < 0.01$, $n = 7$	0.02 (0.01-0.02)	1.13 (0.7-1.8)
	10	59 ± 6			
	30	80 ± 5			
9	30	29 ± 10	yes, $p < 0.01$, $n = 7$	0.22 (0.12-0.33)	0.14 (0.07-0.33)
	100	60 ± 4			
	300	77 ± 8			

[a] Apomorphine was used as a reference dopamine agonist inhibiting the positive chronotropic response induced by stimulation of the right cardioaccelerator nerve at 2-Hz frequency.

amine-like effects. In the present work, the target compound based on 9 bears *n*-propyl groups on the side-chain amino group, consistent with several reports[6] that this N-substitution tends to maximize dopaminergic activity and potency.

Synthesis of 9 (R = R′ = n-C_3H_7) began with a Reissert indole sythesis using 6-chloro-2-nitrotoluene. The 4-chloroindole product was converted into 4-cyanoindole with $Cu_2(CN)_2$.[14] This nitrile was hydrolyzed to indole-4-carboxylic acid, and the *N*-benzoyl derivative of this acid was homologated to indole-4-acetic acid by an Arndt–Eistert sequence. This carboxylic acid was converted to its *N*,*N*-di-*n*-propylamide with di-*n*-propylamine and hexamethylphosphorous triamide/CCl_4. The amide was reduced with $LiAlH_4$ to 9 (R = R′ = n-C_3H_7), which was characterized and evaluated biologically as its bifumarate salt, mp 154–155 °C (EtOH–Et_2O–petroleum ether): MS, *m*/*e* 244 (M^+ – fumaric acid).

Pharmacology. Methods. Inhibition of Postganglionic Cardioaccelerator Nerve in Cats. Anesthesia was induced by intrathorax administration of pentobarbital sodium (30 mg/kg). Arterial pressure was measured from the right femoral artery using a Statham P23AA pressure transducer and was recorded using a Beckman RS dynograph. The pulses were integrated and recorded by use of a cardiotachometer. The respiration was supported by a Harvard respiratory pump and, following a midline incision of the thorax, bipolar platinum electrodes were placed on the right postganglionic cardioaccelerator nerves for stimulation using a Grass S4S stimulator. The frequency of stimulation was 2 Hz. The impulses were delivered from 20–30 s and a pulse duration of 5 ms was used. Supramaximal voltage was used. After the establishment of consistent controls, 1, 2, or 9 was administered to cats in doses that varied by 0.48 log intervals. The ability of 1, 2, and 9 to affect mean arterial pressure and resting heart rate was determined, as well as the ability to inhibit neuronal sympathetic transmission. At the completion of each experiment, 100 μg of haloperidol was administered iv, and the ability of the compounds to inhibit cardioaccelerator nerve stimulation was redetermined.

Inhibition of Spontaneous Locomotion in Rats. Sprague–Dawley rats (225–250 g) were kept in a lighted room for at least 24 h. Pairs of rats were injected sc with 9 (R = R′ = n-C_3H_7) and placed in a darkened room for 30 min and then in a *Plexiglas* container, and locomotion was followed using an electromagnetic activity meter (Columbus Instruments, Model S) for an additional 30 min. The counts recorded during the first 6 min were discarded, and the following 24-min counts were recorded. Six pairs of rats were used for each dose and received either saline (0.9%) or 0.33, 1.0, or 3.3 mg/kg 9 in normal saline.

Renal Vasodilatation Experiments in Dogs. The standard procedure of Goldberg[15] was used for studying the vascular (postsynaptic) effects of the compounds. Pentobarbital-anesthetized dogs were prepared for recording carotid blood pressure and renal artery flow. Various doses of the compounds and dopamine were injected intraarterially in a fixed volume of 0.2 mL.

Statistics. The ID_{50} values for inhibition of cardioaccelerator nerve stimulation and inhibition of locomotion were calculated by the method for probit analysis, and bioassays were analyzed by parallel line assay as described by Finney.[16]

Results and Discussion

The presence of presynaptic dopaminergic receptors inhibiting sympathetic transmission has been well documented.[17] Many compounds possessing dopamine-like properties have been shown to inhibit the positive chronotropic response induced by low-frequency nerve stimulation.[18-23] This neuronal activity involves the stimulation of presynaptic dopaminergic receptors present in the peripheral sympathetic nerve endings, resulting in a decrease of norepinephrine release, an effect blocked by dopamine antagonists. This has been used as a tool for detecting compounds exerting dopaminergic activity.

All of the compounds studied elicited significant dopaminergic activity. Table I shows that lergotrile (1) and 9 were equally active in anesthetized cats in a test for their ability to inhibit neuronal postganglionic cardioaccelerator nerve stimulation. Pergolide (2) was the most active in

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Table II. Cardiovascular Effects of Lergotrile (1), Pergolide (2), and 4-[2-Di-*n*-(Propylamino)ethyl]indole (9) in the Anesthetized Cat

		effect on mean arterial blood pressure		
no.	dose, μg/kg	% increase from resting control[a]	% decrease from resting control	% decrease in heart rate
1	30		22 ± 4	11 ± 3
	100		34 ± 5	10 ± 4
			(97 ± 7)[b]	(152 ± 8)
	300		38 ± 6	12 ± 4
2	3	5 ± 2	5 ± 2	23 ± 3
	10	15 ± 4	8 ± 2	59 ± 6
			(110 ± 12)	
	30	52 ± 17	6 ± 2	80 ± 5
9	30	6 ± 2	11 ± 4	7 ± 2
	100	16 ± 2	18 ± 5	12 ± 2
			(101 ± 4)	(123 ± 13)
	300	41 ± 21	10 ± 4	10 ± 4

[a] The primary pressor effect induced by pergolide (2) and 9 was transient and of short duration. [b] Values within parentheses indicate resting mean arterial blood pressure (mmHg) and resting heart rate (beats/min).

this respect. All compounds lowered mean arterial pressure and resting heart rate. Compound 9 did not antagonize the positive chronotropic responses to epinephrine or isoproterenol, nor did 9 antagonize the vasopressor response to epinephrine. Haloperidol (100 μg/kg) antagonized significantly the inhibition of the cardioaccelerator nerve preparation induced by 1, 2, and 9. In most preparations, the heart-rate reductions and inhibition of neural stimulation induced by 1 and 2 lasted 60 min. Comparable doses of 9 lasted 2–3 h or more.

In rats, 9 induced decreased locomotion during the 24-min period that was measured 6 min after sc administration. The ED_{50} (μmol/kg) and 95% confidence limits are 2.0 (0.33–4.1).

Following iv injection into cats, all compounds studied produced lowering of mean blood pressure, decrease in heart rate (Table II), and inhibition of positive chronotropic responses induced by stimulation of postganglionic fibers of the cardioaccelerator nerves. Compounds 1 and 9 required 30–40 min following iv administration to reach maximal inhibition of neural transmission. This slow rate of onset of action may indicate metabolic activation. The duration of effect of 9 was considerably greater than for 1 and 2. The inhibition by 9 of sympathetic neural transmission to the hearts, as well as the production of bradycardia, was not related to inhibition of β_1 receptors in the heart. The positive chronotropic responses induced by epinephrine or isoproterenol were not inhibited by 9. Likewise, 9 did not antagonize the vasopressor responses to epinephrine, indicating no inhibition of α_1 adrenoceptors of the arterial bed. Haloperidol (100 μg/kg) reversed neural inhibition produced by all compounds, which is evidence that they interact with dopaminergic inhibitory receptors on the adrenergic nerve terminal of cats.

Compound 9 induced decreased locomotion in rats. Whether this reflects synaptic dopaminergic neuronal inhibition in the striatum, or some other mechanism, has not been determined. However, this demonstrates the activity of 9 in a second animal species and indicates that it apparently crosses the blood–brain barrier.

None of the compounds produced renal vasodilatation, in accord with the report of McNay et al.[24] that lergotrile (1) does not dilate the renal vascular bed.

The biological data presented in this communication suggest that 9 (R = R′ = n-C_3H_7) is a dopaminergic agonist. In the anesthetized cat, lergotrile (1) and 9 are quite parallel in their actions and potencies. The data are consistent with the proposal that the structure of 9 is the active pharmacophore in the lergotrile and pergolide molecules. Bach et al.[11] have proposed that the dopaminergic pharmacophore of ergoline is the pyrroleethylamine moiety. This contrast remains to be clarified by further studies.

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