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LY141865, a D_2-dopamine agonist, increases acetylcholine concentration in rat corpus striatum

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Stimulation of dopamine receptors leads to a decrease of acetylcholine (ACh) release (Stadler et al 1973) and turnover (Trabucchi et al 1975; Guyenet et al 1975) and an increase of ACh concentrations in the corpus striatum (McGeer et al 1974). D_2-dopamine (DA) receptors are believed to mediate the tonic inhibitory influence on intrinsic cholinergic neurons in the striatum (Sethy 1979; Euvrard et al 1979; Scatton 1982).

Recent studies have identified a partial ergoline, LY141865, as a D_2-specific DA agonist which stimulates DA receptors without an activation of adenylate cyclase (Tsuruta et al 1981). In agreement with earlier conclusions (Sethy 1979; Euvrard et al 1979; Scatton 1982), we found in the present studies that administration of the D_2 agonist, LY141865, caused an increase of striatal ACh concentrations. In addition, the ergoline DA agonist, pergolide, which activates the striatal adenylate cyclase (Wong & Reid 1980; Goldstein et al 1980), had a similar pharmacological profile of a dopamine agonist as LY141865, but was more potent (Fuller et al 1979; Rabey et al 1981). Pergolide also increased ACh concentrations in striatum. On the other hand, 3-PPP, a putative agonist for the autoreceptors of dopamine (Hjorth et al 1981), did not affect striatal ACh.

Method

Male Sprague-Dawley rats, 100–150 g, were obtained from Harlan Industries, Cumberland, IN, and fed Purina Chow freely for at least three days in a 24 °C room. Pergolide mesylate (8β-[(methylthio)methyl]-6-propylergoline monomethanesulfonate), LY141865 (*trans*-(±)-4a,5,6,7,8,8α,9-octahydro-5-propyl-2H-pyrazole[3,4,-g]quinoline dihydrochloride) and 3-PPP (3-[3-hydroxyphenyl]-*N*-n-propylpiperidine) were injected i.p. and the rats decapitated 30 min later. Striata were rapidly dissected and placed on dry ice before analysis. ACh concentration was determined by radiochemical procedures (Shea & Aprison 1973; Smith et al 1975).

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Results

Table 1 shows the effects of 0·1, 0·3 and 0·6 mg kg^{-1} i.p. doses of LY141865 on ACh concentrations in corpus striatum. These were significantly increased, 29 and 44% respectively, with the two higher doses of LY141865 within 30 min of administration. An average ED50 (dose producing half-maximal response) of 0·5 ± 0·1 mg kg^{-1} i.p. was obtained from three separate determinations. A statistically significant increase of 52% in ACh was also found with the highest dose (0·3 mg kg^{-1} i.p.) of pergolide, and the increase with the two lower doses of pergolide was relatively small (10%). An average ED50 of 0·25 mg kg^{-1} i.p. was estimated for pergolide from two separate determinations. No significant effect of 3-PPP in doses of 10, 30 and 50 mg kg^{-1} i.p. was found in striatal ACh concentrations, while the administration of haloperidol at 5 mg kg^{-1} i.p. brought a 36% decrease. DA-antagonists are known to lower ACh levels (McGeer et al 1974).

Discussion

These data show that LY141865 elevates striatal ACh concentrations, an indication of a decrease of ACh utilization and turnover (Guyenet et al 1975; Trabucchi et al 1975). Two other ergoline dopamine agonists, lergotrile and bromocriptine, also produced increases of ACh levels at relatively high doses of 3 and 10 mg kg^{-1} i.p., respectively (Sethy 1979). These three drugs (LY141865, lergotrile and bromocriptine) have been classified as D_2 agonists since they failed to activate the striatal adenylate cyclase in-vitro (Tsuruta et al 1981; Kebabian & Calne 1979). Therefore, it is consistent with the idea that D_2 receptors are responsible for exerting the inhibitory influence on intrinsic cholinergic neurons in striatum (Sethy 1979; Euvrard et al 1979).

Table 1. Effects of pergolide, LY141865 and 3-PPP on acetylcholine concentractions in rat corpus striatum.

Treatment	Dose mg kg^{-1}	Acetylcholine concn nmol g^{-1} tissue	Percent control
Experiment A			
Control		42·2 ± 3·6	100
LY141865	0·1	45·1 ± 1·9	107
	0·3	54·5 ± 3·0	129*
	0·6	60·9 ± 1·9	144*
Pergolide	0·05	46·2 ± 2·4	110
	0·10	46·4 ± 2·5	110
	0·30	64·3 ± 2·3	152*
Experiment B			
Control		40·1 ± 2·0	100
3-PPP	10	42·4 ± 2·9	106
	30	37·8 ± 2·3	94
	50	40·3 ± 1·4	101
Haloperidol	5	25·8 ± 1·4	64*

* Statistically significant difference from corresponding control values ($P < 0·05$).

LY141865, however, is about half as effective as the erogline, pergolide, in increasing the ACh levels in striatum. The difference in potencies of the two compounds is consistent with their other postsynaptic responses, including turning behaviour in nigrostriatal-lesioned rats (Bach et al 1980; Rabey et al 1981) and the increase in serum corticosterone levels (Fuller & Snoddy 1981; Fuller et al 1982). In other words, the activation of the non-adenylate cyclase-linked D_2 receptors appears to mediate the afore-mentioned postsynaptic responses. The fact that pergolide produces similar responses with greater potency merely suggests the greater affinity of pergolide for these D_2 receptors than LY141865. However, pergolide may not be as selective as LY141865 since pergolide also activated the striatal adenylate cyclase (Wong & Reid 1980; Goldstein et al 1980).

On the other hand, 3-PPP, a putative dopamine presynaptic agonist, failed to produce any effect on ACh levels at doses ranging from 10 to 50 mg kg^{-1} i.p. At a similar dose range, subcutaneous injections of 3-PPP decrease dopamine turnover and locomotor activity without producing stereotyped behaviour (Hjorth 1981). In-vitro, 3-PPP, up to 100 μM concentration, did not activate adenylate cyclase in carp retina (Watling & Williams 1982) or in rat striatal membranes (Wong et al 1983). Therefore, the receptors responsible for the control of dopamine turnover appear to be non-adenylate cyclase-linked. It is highly possible that within the non-adenylate cyclase-linked or D_2 receptors (Kebabian & Calne 1979) there are subtypes of D_2 receptors. LY141865, pergolide, lergotrile and bromocriptine activate the postsynaptic D_2 receptors, including those on intrinsic cholinergic neurons in striatum; 3-PPP represents a separate subtype of D_2 agonists which regulate the autoreceptors of dopamine. Indeed, radioligand binding assays reveal multiple dopamine-sensitive sites, D_3 and D_4 (Seeman 1981), and 3-PPP has been thought to associate with one or both of the latter sites (Wong et al 1983).

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