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Dopaminergic regulation of acetylcholine turnover rate in rat striatum

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Many investigators have proposed that dopaminergic and cholinergic systems interact in striatum and N. Accumbens. The cholinergic neurones in striatum are small interneurones which presumably control and coordinate excitability of efferent and afferent pathways to this nucleus. We know that when activity of cholinergic neurones is reduced the turnover rate of acetylcholine (ACh) is diminished and the concentration of this transmitter may be increased. We have, therefore, decided to measure the steady-state and turnover rate of striatal ACh when the function of dopaminergic neurones was pharmacologically perturbed to study the nature of the relationship between these two neuronal systems. Rats were infused intravenously at a constant rate (30 μCi min^{-1}, kg^{-1}; 1.2 ml) with phosphoryl [Me-^{14}C]-choline and killed after various infusion times with a focused beam of microwave radiation (2.5 kw; 2.45 GHz, 75 mW/cm^2 for 1.8 s) (Guidotti, Cheney, Trabucchi, Doteuchi, Wang & Hawkins, 1974). The change with time of the specific activity of striatal choline (SCh) and ACh (SACh) was not parallel between 0 and 8 min of infusion suggesting that a feedback of radioactive choline into ACh was not operative in these experimental conditions. Hence, a single compartmentation open at both ends was assumed as a kinetic model to estimate striatal ACh turnover rate. From the steady state equation

$$\frac{d\ SACh}{dt} = k_B(SCh - SACh)$$

where k_B is the efflux of SACh from striatum and k_A is the kinetic constant for the conversion of SCh into SACh. In our rats, k_A = 0.29/min and k_B = 0.36/minute. The concentration of striatal ACh was 50 ± 5 nmol/g suggesting a turnover rate of 14.5 nmol g^{-1} minute. Defining

$$m = \frac{SACh\ (t_n)}{SCh\ (t_n)}$$

a table was formed where k_B could be estimated from a single value of m, assuming k_A = 0.29/minute. ACh turnover rate is = k_B[ACh]

m	1.1	1.2	1.5	1.7	2	2.5	3
k_B	1.4	0.88	0.46	0.37	0.27	0.20	0.15

In our drug studies, all the rats were killed at 6 min of infusion. None of the drugs tested changed the steady state of striatal ACh. Apomorphine (4-8-16 μmol/kg) decreased the turnover rate of ACh in a dose related fashion by 20, 40 and 50%, respectively. In the same rats, the turnover rate of striatal ACh was unchanged in the cortex. The inhibition of striatal ACh turnover by apomorphine was completely abolished by pretreating the animals with haloperidol (10 μmol; 1 h before infusion). Dopa (500 μmol/kg 10 min before infusion) decreased the turnover rate in caudate by 50% without any change in the cortex. Haloperidol (10 μmol) increased the turnover rate of striatal ACh, chlorpromazine was less active, clozapine was inactive. The interactions between benztropine and haloperidol were also studied. They suggest that clozapine may be inactive because it blocked the muscarinic receptors. From these studies, it appears that dopamine exerts an inhibitory action in the activity of cholinergic neurones of striatum. Our experiments also suggest that the activity of the striatal cholinergic neurones may have a stimulatory cholinergic input impinging upon a muscarinic receptor.

Reference

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Dopaminergic-cholinergic interaction in the striatum: decrease in rat striatal acetylcholine (ACh) levels by dopaminergic and cholinergic antagonists

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We recently reported that pimozide, a powerful neuroleptic dopaminergic antagonist, decreased rat striatal acetylcholine (ACh) levels (Ladinsky, Consolo & Garattini, 1974). Many other drugs have now been found to produce a decrease in rat striatal ACh. The approximate order of potency for the drugs studied were: haloperidol = pimozide $\geqslant$ reserpine $\ggg$ chlorpromazine $\geqslant$ 1-fenfluramine $\geqslant$ clozepine $>$ sulpyrid. Haloperidol (0.5 mg/kg) produced a 50% decrease in striatal ACh 15 min after administration. ACh levels remained markedly reduced 16 h later. The effect of haloperidol on ACh levels in various brain areas demonstrated that when the striatal levels were decreased by 50%, there was only a 17% decrease ($P = 0.05$) in the diencephalon and no effect in the mesencephalon, cerebellum or hemispheric rest after removal of the striatum. Choline levels were significantly decreased in the diencephalon by haloperidol and in the striatum by pimozide.

Striatal choline acetyltransferase and acetylcholinesterase were not affected by these agents after *in vivo* administration or *in vitro* incubation.

The anticholinergic agent, trihexyphenidyl (10 mg/kg) caused a sharp drop in striatal ACh (Consolo, Ladinsky & Garattini, 1974) which was limited only to the striatum and hemispheric rest, there being no effect in the diencephalon, mesencephalon or cerebellum.

It is suggested that the neuroleptics decrease striatal ACh through direct blockade of striatal dopaminergic receptors resulting in disinhibition of striatal cholinergic interneurones and a marked release of ACh. The anticholinergic agent is suggested to produce its effect through blockade of striatal cholinergic receptors resulting in negative feedback of nigro-striatal dopaminergic neurones, causing again, disinhibition of the cholinergic neurones. This would be in agreement with the decreased turnover of cerebral dopamine caused by atropine (Bartholini & Pletscher, 1971) and by trihexyphenidyl (Anden & Bedard, 1971).

References

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