Is metoclopramide a directly acting dopamine receptor antagonist?

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Metoclopramide produces a blockade of cerebral dopamine (DA) receptors as judged by behavioural (Costall & Naylor, 1973; Dolphin, Jenner, Marsden, Pycock & Tarsy, 1975) and biochemical studies (Ahtee & Buncombe, 1975; Peringer, Jenner & Marsden, 1975). The blockade is presumed to account for the acute dyskinesias produced in man by metoclopramide, by analogy to the classical neuroleptic agents. Metoclopramide, however, has no apparent antipsychotic activity suggesting that its mode of action differs from that of neuroleptic drugs.

Administration of metoclopramide (10-100 mg/kg i.p.) to male mice 1.5 h prior to killing produced a similar dose-dependent increase in both striatal and mesolimbic homovanillic acid (HVA) levels. Levels of dihydroxyphenylacetic acid (DOPAC) in striatum and mesolimbic areas were only elevated after metoclopramide 100 mg/kg i.p. Metoclopramide (50 mg/kp i.p.) enhanced the α-methyl-*p*-tyrosine (200 mg/kg 2 h prior to killing; AMPT) induced fall in whole brain DA levels (AMPT treated 385 ± 57 ng/g; metoclopramide treated 171 ± 23 ng/g; $P < 0.005$). Similarly, metoclopramide (50 mg/kg i.p.) enhanced the NSD 1034 (*N*-[3-hydroxybenzyl]-*N*-methylhydrazine dihydrogen phosphate; 150 mg/kg 0.5 h prior to killing) induced accumulation of whole brain DOPA (NSD 1034 treated 496 ± 128 ng/g; metoclopramide treated 1212 ± 182 ng/g; $P < 0.01$). This evidence suggests that metoclopramide increases the synthesis and release of DA. By analogy to the classical neuroleptic drugs, these biochemical changes may be due to functional blockade of cerebral DA receptors suggested by the behavioural studies.

The *in vitro* rat striatal DA sensitive adenylate cyclase system was stimulated approximately two-fold by the addition of DA 10^{-4} M (23.8 to 56.8 pmoles cyclic AMP/2 mg tissue wet wt/2.5 min). Addition of metoclopramide 10^{-7} to 10^{-4} M, however, did not inhibit the stimulation of striatal adenylate cyclase by DA (10^{-4} M).

Ten minutes after injection of metoclopramide (100 μg in 3 μl 0.9% NaCl solution, saline) into one striatum of rats, apomorphine (1 mg/kg i.p.) produced tight circling towards the injected striatum. Injection of 0.9% saline (3 μl), or procaine hydrochloride (100-200 μg in 3 μl 0.9% saline), into one striatum followed by apomorphine (1 mg/kg) was without effect.

This data suggests that the blockade of DA receptors observed following administration of metoclopramide is due to a specific central action of the drug itself, rather than to a peripheral metabolite. However, the failure of metoclopramide to inhibit the DA sensitive adenylate cyclase system *in vitro* suggests a mode of action differing from that of antipsychotic drugs. Whether this represents an action on other DA receptors not tested by the *in vitro* system, or an effect on another neuronal system remains to be determined.

References

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