Effect of drugs on metoclopramide-induced catalepsy and increase in striatal homovanillic acid content

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Metoclopramide disturbs the extrapyramidal control of motor functions in man (Casteels-Van Daele, Jaeken, Van Der Schueren, Zimmerman & Van Den Bon, 1970) and in rats (Costall & Naylor, 1973). In mice metoclopramide-induced catalepsy is associated with a nearly five-fold elevation of striatal homovanillic acid (HVA) content (Ahtee & Buncombe, in press). In the present experiments the mechanism of the cataleptic action of metoclopramide was studied by using drugs, which alter the dopaminergic or cholinergic activity or the content of γ-aminobutyric acid (GABA) in the central nervous system.

Female Wistar rats (180-220 g) were used. Catalepsy was scored by using four tests (3 cm high bar, 9 cm high bar, parallel bars, and vertical grid); each test was scored from 0 to 2. The scores of the four tests were added. The striata of two brains were pooled for the spectrophotofluorimetric estimation of HVA. Metoclopramide and apomorphine were injected s.c., atropine and aminooxyacetic acid (AOAA) i.p.

The dose of 20 mg/kg of metoclopramide induced in rats catalepsy which was maximal at 2-3 h after injection. Apomorphine (10 mg/kg) and atropine (50 mg/kg) significantly reduced the cataleptic effect of metoclopramide. AOAA (25 mg/kg) potentiated the cataleptic effect of 5 mg/kg of metoclopramide. The dose of 20 mg/kg of metoclopramide caused a six-fold elevation of striatal HVA content, but did not alter the brain dopamine content. Apomorphine decreased the striatal HVA content by 66-69% ($p < 0.01$) both in control and in metoclopramide-treated rats. Atropine or AOAA did not alter the metoclopramide-induced elevation of striatal HVA content.

The increased HVA and unchanged dopamine content in the brain of metoclopramide-treated rats suggests that dopamine formation is increased. Thus metoclopramide could act as has been suggested for the neuroleptic compounds (Carlsson & Lindqvist, 1963) by directly blocking the striatal dopaminergic receptors, whereafter a neuronal feedback mechanism could increase the production of dopamine. This assumption is supported by the finding that apomorphine, a drug which is thought to stimulate the dopaminergic receptors, antagonized both the cataleptic and HVA increasing effects of metoclopramide. Moreover, AOAA, a drug which increases the concentration of GABA which is thought to have an inhibitory influence on dopaminergic striatal neurons, potentiated the metoclopramide-catalepsy. However, the mechanism of metoclopramide-catalepsy seems to be somewhat different from the catalepsy induced by neuroleptic compounds, because atropine antagonized the catalepsy but not the HVA increase produced by metoclopramide, whereas atropine is known to antagonize both the catalepsy and HVA increase produced by neuroleptic compounds (Andén & Bédard, 1971; O'Keeffe, Sharman & Vogt, 1970).

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