Comparative studies on the effects of metoclopramide and some known neuroleptics on the EEG of the conscious rat

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Like the clinically used neuroleptics, metoclopramide, an anti-emetic, when given to laboratory animals induces catalepsy (Ahtee, 1975), antagonizes apomorphine-induced stereotypy and amphetamine-induced ipsiversive circling (Dolphin, Jenner, Marsden, Pycock & Tarsy, 1975) and increases brain homovanillic acid concentrations (Peringer, Jenner & Marsden, 1975). However, it has apparently little neuroleptic action in man (Borenstein & Bles, 1965). The predictive value of these animal tests being in question we considered it of interest to compare metoclopramide with three clinically used neuroleptics (chlorpromazine, haloperidol and pimozide), with regard to their effect on the electroencephalogram (EEG) and on dexamphetamine-induced alerting of the EEG in the conscious rat.

EEG studies were undertaken in rats (male, 250 to 350 g) chronically implanted with skull electrodes (Goff, Miller, Smith, Smith and Wheatley, 1975). The parietal EEG, recorded on magnetic tape was analysed for 10 s periods at 10 s intervals by passing it through four broad wave band filters which measured the voltage within each of the following frequency bands (FB): 2.4 to 4.0, 4.0 to 7.5, 7.5 to 13.5 and 13.5 to 26.0 Hz (FB1 to FB4 respectively). The hourly mean integrated voltages were calculated. The neuroleptics were injected subcutaneously at the ED_{95} values found to antagonize the stereotypy induced 30 min after apomorphine (5 mg/kg s.c.) in tests in which they were administered 60 min previously; similar doses antagonized dexamphetamine-induced (5 mg/kg s.c.) stereotypy.

In the EEG studies with drugs alone the mean hourly voltages in the 4 h period after drug administration were compared with the mean value for the preceding 2 h control period. Chlorpromazine (8.4 mg/kg, $n=3$) increased ($P \leqslant 0.05$) total voltage and voltages in each FB at all times. Haloperidol (1.3 mg/kg, $n=3$) increased ($P \leqslant 0.05$) total FB3 and FB4 voltages from 2 to 4 h but metoclopramide (17.0 mg/kg, $n=3$) and pimozide (1.7 mg/kg, $n=3$) like the control vehicle ($n=9$), had no effect.

In the EEG studies of dexamphetamine-induced alerting, the neuroleptics, or control vehicle, were injected at the end of a 2 h control period and 1 h before dexamphetamine (0.3 mg/kg s.c.). In control rats ($n=5$) this dose of dexamphetamine had no gross behavioural effects but showed a significant reduction in total voltage for the first hour only ($P=0.05$). This alerting effect was antagonized by chlorpromazine, haloperidol and pimozide ($n=3$ or 4) but was prolonged by metoclopramide ($n=5$) with voltage being significantly reduced at both 1 and 2 h ($P \leqslant 0.03$).

Dexamphetamine's altering action may be attributable to noradrenaline release in the brain stem (Boakes, Bradley & Candy, 1972) and its antagonism by chlorpromazine and haloperidol may reflect their ability to block noradrenaline receptors in addition to their blockade of dopamine receptors (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970). However, there is no obvious correlation between the effects of the neuroleptics on dexamphetamine-induced EEG alerting and their ability to block catecholamine receptors as both pimozide and metoclopramide which block dopamine but not noradrenaline (Andén *et al.*, 1970; Peringer *et al.*, 1975) had contrasting actions. The potentiation of dexamphetamine by metoclopramide may be explained by inhibition of dexamphetamine or noradrenaline metabolism.

Additionally, our studies suggest that tests for blockade of dexamphetamine-induced EEG alerting may perhaps be of more value than others in predicting clinical usefulness of neuroleptics.

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