The effect of co-administration of the antacid preparation on the AUC of ranitidine in fasted subjects was similar but greater than that with cimetidine. The decrease of 59% was comparable to that reported by Mihaly et al (1982). In a different group of subjects, consumption of breakfast abolished the effect of the antacid preparation on AUC of ranitidine.

The AUC of a drug may be affected by its absorption or its elimination. If the latter were the case, the $t_{\frac{1}{2}}$ would be expected therefore to diminish, but no consistent effect of antacid on $t_{\frac{1}{2}}$ was found. It is therefore likely that the differences in AUC reflect changes in absorption. Other values which may be expected to reflect changes in absorption, such as K_{up}, the slope of the upstroke of the concentration-time curve, or C_{max} or T_{max}, were not reproducibly affected by either antacid or food. However, a double peak in the plasma-concentration time curves for both cimetidine and ranitidine was seen in most subjects. This is consistent with the observations made by Mihaly et al (1980a) and it may have obscured changes in the curves.

A likely explanation of these results is that the presence of the antacid impairs dissolution of the tablets or that the dissolved drug is bound to the unabsorbed antacid. The abolition of antacid effects in the presence of food could be due to competition for drug binding sites on the antacid gel. The study indicates that antacids of the type used should not be taken in close proximity to H_2- receptor antagonists.

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J. Pharm. Pharmacol. 1990, 42: 354–355
Communicated January 4, 1990

Chronic administration of MK-801 and the NMDA receptor: further evidence for reduced sensitivity of the primary acceptor site from studies with the cortical wedge preparation

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Abstract—Cortical slices removed from rats pre-treated with MK-901 0.5 mg kg^{-1} twice a day for 7 days had reduced responses to *N*-methyl-D-aspartate (NMDA) relative to quisqualate and glutamate compared with control animals. Potencies of competitive (CPMP) and non-competitive (ketamine) NMDA antagonists appeared unchanged. These changes are consistent with a reduced density of NMDA receptors.

MK-801 ((+)-5-methyl-10, 11-dihydro-5H-dibenzo-[a, d] cyclo-hepten-5, 10-imine) has recently attracted considerable attention because it protects against neuronal degeneration following ischaemic and hypoglycaemic episodes. Additionally, MK-801 readily crosses the blood-brain barrier and is a potent anticonvulsant (see Manallack et al 1988, 1989). MK-801 has many actions in common with phencyclidine (PCP)-like molecules (Manallack et al 1988) and acts via the PCP site in the ionophore of the *N*-methyl-D-aspartate (NMDA) subtype of L-glutamate (Glu) receptor to produce a "use-dependent", non-competitive blockade (Davies et al 1988b). Recently, to gain insights into the regulation of the NMDA receptor, we studied the effects of the chronic administration of MK-801 on various indices reflecting the functioning of the domains of the NMDA receptor (Manallack et al 1989). Despite behavioural tolerance to the actions of MK-801, neither the number nor density of PCP site was altered, whilst there was a down-regulaton (50% decrease) of cortical sites for [^{3}H]-D-2-amino-5-phosphonopentanoic acid. These data suggested differential regulation of the domains of the NMDA receptor and adaptations of the primary acceptor site for agonists/antagonists in response to MK-801 treatment. To provide further insight into functional adaptations of the NMDA receptor-ionophore complex we have investigated the effects of chronically administered MK-801 using the "cortical wedge" preparation.

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Methods and results

Male Sprague-Dawley rats (200-250g) received intraperitoneal injections of MK-801 as previously described (2 × daily, 0·5 mg kg^{-1}, 7 days), except that the interval between the last injection

Table 1. Response ratios for excitatory amino acids in the cerebral cortex from control and MK-801 treated rats.

	$NMDA_{20}/Quis_{20}$	$NMDA_{40}/Quis_{40}$	$Glu_1/Quis_{20}$	$Glu_2/Quis_{40}$	$NMDA_{20}/Glu_1$	$NMDA_{40}/Glu_2$
Control	1·73±0·16 (13)	1·82±1·14 (13)	1·13±0·08 (12)	1·14±0·09 (12)	1·40±0·13 (12)	1·83±0·19 (12)
MK-801	1·58±0·28 (7)	1·18±0·18* (10)	1·16±0·22 (11)	1·09±0·22 (10)	1·14±0·30 (7)	1·52±0·30 (11)

Responses were obtained using the cerebral cortical wedge preparation and NMDA 20 and 40 μM, L-glutamate (Glu) 1 and 2 mM, and quisqualate (Quis) 20 and 40 μM. Values are mean ± s.e.m. of number of observations made with cortical wedges indicated in parenthesis. *$P < 0.01$. (Student's t-test).

and killing the rats was 24 h to allow greater "washout" of this lipophilic drug (Manallack et al 1989). Brains were rapidly removed and cortical wedges were cut freehand from the anterior cingulate cortex of coronal, 400 μm Vibratome sections. Details of these methods and the use of the cortical wedge preparation to monitor depolarizing responses to excitatory amino acids (EAAs) and the actions of antagonists can be found elsewhere (Davies et al 1988b). Depolarizations were recorded as d.c. potential, amplified and displayed on a pen recorder. Response ratios were determined after measuring peak heights for agonists. Responses to sequential applications of two concentrations of three EAAs were examined and response ratios were determined for each slice preparation (Table 1) to normalize data thus allowing for daily variations and differential sensitivities—additionally quisqualate-induced responses should be unaffected by the regime of MK-801. The concentrations of EAAs employed were chosen on the basis of previous experience and produced submaximal responses. NMDA/quisqualate ratios were found to be significantly lower ($P < 0.01$) in the slices from rats treated with MK-801 at higher agonist concentrations. There was also a trend for the NMDA/quisqualate ratio to be decreased in MK-801 treated preparations at lower agonist concentrations; pooling all NMDA/quisqualate data (Table 1) gave the following response ratios: control 1·77±0·10 (26) and MK-801 1·35±0·16 (17; $P < 0.05$). Response ratios for Glu/quisqualate and NMDA/Glu were not significantly altered. These data suggest that only the response to NMDA is altered by the treatment with MK-801 and that this differential effect on NMDA becomes more apparent in the upper part of the dose response curve.

Other experiments were performed to determine whether the schedule of MK-801 had altered the abilities of competitive and non-competitive NMDA antagonists to attenuate responses to NMDA (40 μM). Data obtained from these experiments were subjected to log-probit analyses to provide estimates of IC50 values and the slopes of the lines describing the inhibition data. 3-(2-Carboxypiperidin-4-yl) methyl-1-phosphate (CPMP), a competitive NMDA antagonist (Lodge et al 1988), appeared to be equi-effective in the cortical wedges from both control and MK-801 treated rats: control IC50 1·5±0·10 μM, slope −0·99±0·08 (23 observations); MK-801 IC50 1·7±0·21 μM, slope −0·84±0·14 (23 observations). As previously reported the actions of ketamine were use-dependent (Davies et al 1988b), but the schedule of MK-801 failed to affect the blockade of NMDA-induced responses by ketamine: control IC50 4·3±0·53 μM, slope −0·56±0·16 (14 observations); MK-801 IC50 5·6±0·81 μM, slope −0·94±0·26 (15 observations). However, there was a trend for ketamine to be a less effective antagonist at higher concentrations (note slopes from IC50 analysis). Both CPMP and ketamine failed to attenuate responses induced by quisqualate.

Discussion

The chronic regime of MK-801 altered the sensitivity of the primary acceptor site of the NMDA. Specifically, depolarizing responses to NMDA were reduced by 1/3 relative to control, while responses to quisqualate and glutamate were unaffected. The result with glutamate was not unexpected as its action in the cortical wedge may be unrelated to the NMDA receptor and is relatively insensitive to NMDA antagonists (Davies et al 1988a). Although there are likely to be more problems with residual drug in the present experiments relative to our previous studies in well-washed membranes, we attempted to address this problem by extending the washout time after the final injection from 12 h to a 24 h interval. We have no specific information relevant to the residual levels of MK-801, but indirect evidence that residual drug did not account for the reduced responses to NMDA was that the affinities of non-competitive and competitive antagonists for their binding sites were unaltered by the schedule of MK-801. Overall these findings concur with our previous observations, and the altered NMDA sensitivity is consistent with a reduced density of NMDA receptors (Manallack et al 1989). Clearly further insights are needed into the adaptive responses of NMDA receptors to drug schedules given their considerable clinical relevance.

P.M.B. was the recipient of a Wellcome-Ramaciotti Travel Grant and acknowledges the hospitality of the staff of the R.V.C. Supported in part by a Programme Grant from the N.H. & M.R.C. (Australia). MK-801 was generously donated by Merck, Sharp and Dohme, Harlow, UK.

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