used: GABA (0.1, 0.2 M; pH 3), glycine (0.5 M; pH 3), L-glutamate (0.5 M; pH 7.5), DL-homocysteate (DLH, 0.2 M; pH 7.5), acetylcholine hydrobromide (ACh, 0.25 M), BMC (10 mM in 165 mM NaCl) and sodium pentobarbitone (20 mM; pH 9.5 or 250 mM in a 7 : 2 : 1 mixture by volume of water, propylene gycol and ethanol).

In confirmation of Bowery and Dray[1], pentobarbitone (10–60 nA) partially reversed the antagonism by BMC of the inhibition of cell firing by GABA. With most neurones, however, in the absence of BMC, pentobarbitone ejected with the same or even lower electrophoretic currents enhanced submaximal inhibition of firing by GABA. Furthermore, the inhibitory action of electrophoretic glycine on many cells was also enhanced, but not to the same extent as that of GABA.

Results from one neurone are illustrated by the records in Fig. 1 of the rate of firing of a dorsal horn interneurone maintained by the continuous ejection of DLH, 8 nA. Firing was inhibited by glycine and GABA, ejected consecutively each for 7 s at fixed time intervals (Fig. 1*a*). During the ejection of BMC, the effect of GABA was reduced (Fig. 1*b*), but was restored to near control values during the simultaneous administration of pentobarbitone from an aqueous solution (Fig. 1*c*). This effect of pentobarbitone was reversible (Fig. 1*d*), as was the antagonism of GABA by BMC (Fig. 1*e*). Several minutes later, when the currents ejecting glycine and GABA had been reduced, in particular that of GABA to reproduce the inhibitory action observed during the ejection of BMC (compare Figs 1*b*, *d* and *f*), pentobarbitone also reversibly enhanced the effectiveness of GABA (Fig. 1*g* and *h*). The degree of enhancement of the GABA effect by pentobarbitone in the absence of BMC was very similar to that during the ejection of BMC.

Effects such as these, which were observed with spontaneously active cells as well as with those in which firing was maintained with DLH, glutamate or ACh, and irrespective of the anaesthetic used or whether BMC was in one of the barrels of the micropipettes, render unnecessary a postulate that pentobarbitone displaces BMC from receptors on central neurones[1]. At least in the spinal cord of the cat the increased effectiveness of GABA by pentobarbitone probably is adequate to account for the reversal of antagonism by BMC. Further experimentation will be required to determine whether this action of pentobarbitone results from interference with the cellular uptake of amino acids or from a more direct effect at postsynaptic receptors[3]. The importance of this latter type of action is suggested by the frequent observation that electrophoretic pentobarbitone depressed the firing rate of neurones, and that pentobarbitone, like GABA, depolarises the terminals of group Ia afferent fibres in the cat cord (our unpublished work).

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BOWERY and DRAY reply—The results of Lodge and Curtis are most interesting but, whilst we do not dispute that enhancement of responses to GABA and glycine can occur in the absence of bicuculline methochloride (BMC), in our experiment in the rat medulla we saw no clear enhancement of submaximal responses to GABA or glycine using expelling currents of pentobarbitone which on the same cells reversed the antagonism produced by BMC or strychnine. Pentobarbitone in all cases did not decrease the background firing rate of the cell, an observation which differs from that of Lodge and Curtis. Only when we increased the ejecting current by 2–3-fold did pentobarbitone decrease the firing rate[1]. It remains to be seen whether this decrease in firing results from a GABA-mimetic effect at post-synaptic receptors. It is interesting to note that the increase in firing rate produced by BMC in the Lodge and Curtis experiment (shown in their Fig. 1*b*) seemed to be antagonised by the ejection of pentobarbitone (*c*).

Although Lodge and Curtis suggest that the enhancement of responses to GABA could account for the observed BMC reversal on dorsal horn interneurones in the cat spinal cord we believe that under our experimental conditions on spontaneously-active neurones in the rat medulla, these phenomena are separable. Some evidence in support of this comes from results we have obtained with other drugs in the superior cervical ganglion. Although the barbiturates were the most effective in reversing BMC antagonism other central depressant drugs with quite different chemical structures, for example, benzodiazepines, amitriptyline and promethazine also reduced BMC antagonism. None of these substances significantly potentiated the effect of GABA at the concentrations employed nor did they exhibit any direct GABA-mimetic activity even at >10-fold higher doses.

Experiments with nipecotic acid in the ganglion indicate that BMC reversal by pentobarbitone is probably unrelated to any inhibition of the cellular uptake of GABA. Nipecotic acid inhibits GABA uptake in this tissue and thus potentiates the response to GABA[2]. Unlike pentobarbitone, however, nipecotic acid will neither prevent nor partially reverse BMC antagonism and moreover will not prevent pentobarbitone reversing the action of BMC.

Two phenomena associated with the action of pentobarbitone in relation to GABA and glycine receptors have been described—first, an enhancement of the action of GABA or glycine as reported by Lodge and Curtis and others[3,4] and second, a direct GABA-mimetic action as described by Nicoll[4]. Our results suggest that a third phenomenon may occur, that of reversal of the action of convulsants which antagonise responses to GABA and glycine.

Although separation of these phenomena may not be easy in some systems our results indicate that it is possible in the rat medulla and sympathetic ganglion and may depend on the concentration of pentobarbitone employed.

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