exogenous GABA which adds to the endogenous GABA that is released by the continuous activity of Purkinje cells. After diazepam, the spontaneous firing rate of Purkinje cells is markedly reduced[2,8]. This must result in disinhibition of Deiters' neurones and in the reduction of the total amount of GABA (exogenous plus endogenous) acting on them. The validity of our reasoning could easily be checked experimentally.

Any interpretation of the results of Steiner and Felix[1] on cerebellar Purkinje cells must remain highly speculative when taking into consideration that four of the five types of cerebellar cortical neurones are believed to be GABA-ergic and that the activity of the Purkinje cell is itself inhibited by GABA-ergic interneurones. In the experiments of Steiner and Felix[1] the benzodiazepines did not seem to depress the firing rate of Purkinje cell, whereas in our own experiments[2,8] several representatives of this class of compounds regularly and markedly reduced the spontaneous discharges and strongly antagonised the opposite effect of bicuculline. We should also like to emphasise that the experiments of Steiner and Felix[1] were performed on anaesthetised animals and a multitude of interactions between anaesthetics and benzodiazepines have been described.

In conclusion, it seems that the findings of Steiner and Felix[1] do not fail to support a facilitating effect of benzodiazepines on GABA-mediated transmission[2] but rather that they are easily explained by such a mode of action.

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Steiner and Felix Reply—The hypothesis advanced by Haefely *et al.*[1] that benzodiazepines facilitate GABA-responsive neurotransmission is based on the premise that GABA is the proven mediator of inhibition at presynaptic sites (this is still controversial, see refs 2 and 3) as well as on the demonstration

Matters arising

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that the action of the presumptive GABA antagonists bicuculline and picrotoxin is reduced by this class of psychotropic drugs. Haefely *et al.*[1] are justified in pointing out that the mode of action of centrally acting drugs is bound to be complex and that more than one level of interaction ought to be considered. They fail to mention, however, that so far, there is no direct experimental support for their contention at any level of organisation tested: Neither their own work, nor that of others cited in support of their view, has directly tested GABA-mediated transmission, and thus all their experimental evidence is circumstantial. It was precisely for this reason that we chose to test their hypothesis at the level of identified Purkinje cells and Deiters' neurones[4]. At both these sites, there is incontrovertible evidence for GABA-mediated inhibition, the extent of which can readily be followed by standard electrophysiological techniques. In this anatomically and functionally well defined system, our results indicated that benzodiazepines inhibit GABA-responsive transmission[4]. We remain convinced that our technique is adequate to study the problem, and welcome this opportunity to answer questions raised by Haefely *et al.*[1] about our approach.

For the orthodromic activation of Deiters' neurones by stimulation of Purkinje cell axons, we deliberately chose supramaximal parameters (trains of three pulses of 250 μs duration at 500-μs intervals and an intensity of 0.8 mA). Although we do not refute the view expressed[1] that this type of stimulations is likely to have repercussions on the cerebellar cortex as well as on nerve endings at the level of the Deiters' nucleus, we believe that, as in other biological systems, orthodromically stimulated transmitter release is a direct function of the stimulus applied (and therefore, in our case, a constant); we cannot accept their view that the amount of GABA released in our experimental conditions is modified, in any important respect, by way of the soma of the Purkinje cells itself. With respect to the methodology used, we concede that in any study using microelectrophoresis, the quantity of exogenous neurotransmitter administered, albeit small in absolute terms, is likely to be in the pharmacological range. Changes in endogenous GABA release would therefore seem negligible compared with the amount of exogenous GABA administered. Haefely *et al.*[1] argue that a drop in endogenous GABA release by Purkinje cells (which, in keeping with their hypothesis, they ascribe to a facilitation of GABA-mediated inhibition by benzodiazepines at this site) could "easily" be distinguished from the fixed amount of exogenous GABA applied; in our view, this would require the direct monitoring of GABA release at Purkinje cell terminals on Deiters' neurones and could not reliably be deduced from the rate of cell firing alone (to our knowledge, such microtechniques are presently beyond our reach).

If Haefely *et al.* were correct in their assumption that benzodiazepines facilitate GABA-mediated inhibition at the Purkinje cell (and so reduce their GABA release), they would also have to concede a similar synergism at the GABA-responsive synapses impinging on the Deiters' neurones themselves; if their argument is taken to its logical conclusion, one would have to postulate that reduced GABA release at this site is counteracted, and possibly cancelled out, by an increase in its biological effect. This assumption, however is not borne out by our findings. Likewise, we consider the absence of benzodiazepine effects on the spontaneous rate of discharge of Purkinje cells as further evidence that our findings are not secondary to changes in the extent of excitation of the cerebellar cortex or the use of anaesthetised animals but are a reflection of drug interaction occurring at the site of study itself.

Our results, as well as those of Gähwiler[5], obtained in simple well defined systems, indicate a functional antagonism between GABA and benzodiazepines. They do not confirm the notion of a synergism inferred from indirect observations on more complex structures.

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