Effects of viloxazine on cortical neurone responses to monoamines and acetylcholine

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Viloxazine hydrochloride (ICI 58,834; Vivalan, ICI Ltd.) is a substance belonging to a series of novel psychotropic compounds (Grrenwood, Mallion, Todd & Turner, 1975) and has been found to be a clinically effective antidepressant drug (Peet, 1973; Pichot, 1975). Previous pharmacological studies indicate that viloxazine inhibits the neuronal uptake of noradrenaline (NA) and to a much lesser extent 5-HT but, in contrast to tricyclic antidepressants, it possesses little or no peripheral cholinolytic activity (Greenwood, 1975; Lippmann & Pugsley, 1976). We have used the technique of microiontophoresis to investigate the interactions of this drug with NA, 5-HT and acetylcholine (ACh) on the spontaneous activity of cortical neurones.

Single spontaneously active neurones were studied in the somatosensory cortex of the halothane anaesthetized rat. The techniques used have been described elsewhere (Bradshaw, Roberts & Szabadi, 1974). Repeated responses to NA, 5-HT and Ach were compared before and after the brief application of viloxazine (20–100 nA, 20–50 s).

Following the application of viloxazine, responses to all three agonists were either potentiated or reduced in size. Both effects often occurred in the same study, reduction of response invariably preceding potentiation. The time course for these effects typically showed reduction of response occurring during the first 5–10 min after viloxazine application followed by potentiation of response over the next 15–40 minutes. These effects are similar to those reported for imipramine, desipramine and iprindole where reduction of response followed high doses and potentiation low doses of antidepressant (Bradshaw *et al.*, 1974; Bevan, Bradshaw & Szabadi, 1975a, b).

Since viloxazine can block amine uptake mechanisms (Greenwood, 1975; Lippmann & Pugsley, 1976) the potentiation of NA and 5-HT responses can be explained. The reduction of NA and 5-HT responses possibly indicates that viloxazine in common with tricyclics possesses adrenolytic and anti-5-HT properties.

The effects on Ach responses were less explicable. Bevan *et al.* (1975a) explained the potentiation of Ach responses by impramine and desipramine in terms of the postsynaptic blockade of 'masked' inhibitory receptors. This would not seem to be a satisfactory explanation for the potentiation of Ach responses by viloxazine since it has been reported to have little or no cholinolytic activity. However, since ACh responses of single cells could be reduced by viloxazine, it may be that CNS receptors for Ach are more susceptible to blockade by viloxazine than those studied in the periphery and it is of interest that viloxazine antagonizes oxotremorine-induced hypothemia but not tremor or salivation (Lippmann & Pugsley, 1976).

An action of viloxazine on the inactivation of Ach would also seem possible, i.e. cholinesterase activity may be reduced or the re-uptake process for Ach proposed by Liang and Quastel (1969) may be blocked. There is no evidence, however, that viloxazine has either of these actions.

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