*Br. J. Pharmac.* (1976), **57**, 152–154

# POTENTIATION BY DESIPRAMINE OF NEURONAL RESPONSES TO MESCALINE

P. BEVAN,[1] C.M. BRADSHAW[2] & E. SZABADI[3]
Department of Psychiatry, University of Edinburgh, Morningside Park, Edinburgh EH10 5HF

The effect of desipramine on responses of single cortical neurones to mescaline was studied by the microelectrophoretic technique. Both potentiation and antagonism of responses to mescaline by desipramine were observed. The antagonism may be related to the $\alpha$-adrenolytic action of desipramine. The potentiation is unlikely to reflect the uptake blocking action of desipramine, since desipramine does not block the uptake of mescaline in the cerebral cortex. It is suggested that the potentiation may be due to a post-synaptic action of desipramine.

**Introduction** It is well known that the tricyclic antidepressant drugs (e.g. imipramine and desipramine) block the uptake of monoamines into nerve terminals (Horn, Coyle & Snyder, 1971). The drugs also potentiate pharmacological responses to the monoamines in the periphery and in the central nervous system (Sigg, Soffer & Gyermek, 1963; Bradshaw, Roberts & Szabadi, 1974). Although it is widely believed that there is a causal relationship between these two phenomena (Iversen, 1974), we have recently presented evidence that potentiation of responses to the monoamines can occur in situations where uptake blockade is unlikely to operate. For instance, desipramine can potentiate neuronal responses to noradrenaline and dopamine in the caudate nucleus (Bevan, Bradshaw & Szabadi, 1975a), although it does not block the uptake of catecholamines in this structure (Horn *et al.*, 1971). Furthermore, iprindole, a tricyclic antidepressant with little uptake-blocking activity (Ross, Renyi & Ögren, 1971) is effective in potentiating the responses of single cortical and caudate neurones to monoamines (Bevan, Bradshaw & Szabadi, 1975b). In this paper we give further evidence that uptake blockade is not a necessary condition for potentiation of neuronal responses to the monoamines.

We have previously reported that the hallucinogenic monoamine mescaline (3,4,5-trimethoxyphenylethylamine), applied by microelectrophoresis, can evoke responses in cortical neurones which are similar to those evoked by noradrenaline (Bevan, Bradshaw, Roberts & Szabadi, 1974). It is known that mescaline has an extremely low affinity for uptake mechanisms in the periphery (Iversen, 1967). Moreover, it has recently been reported that although mescaline is accumulated into cortical synaptosomes by an active process, this uptake is not affected by desipramine (Bevan, 1975). In the present study we examined whether neuronal responses to mescaline can be potentiated by desipramine.

[1, 2, 3] Present address: Department of Psychiatry, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT.

**Methods** Single spontaneously-active neurones were studied in the cerebral cortices of cats and rats anaesthetized with halothane. All the drugs were applied by microelectrophoresis. Our techniques for the surgical preparation of the animals, for the extracellular recording of action potentials and the microelectrophoretic application of drugs from six-barrelled micropipettes have been described elsewhere (Bradshaw *et al.*, 1974; Bevan *et al.*, 1974; 1975a; 1975b). The micropipettes contained the following drug solutions: 4M NaCl (two barrels: one for recording, one for current balancing); 0.05M mescaline hydrochloride (pH 4.0); 0.05M noradrenaline bitartrate (pH 3.5); 0.05M sodium glutamate (pH adjusted to 8.5 with NaOH); 0.15M desipramine hydrochloride (pH 4.5). Repeated responses to mescaline were compared before and after a brief application of desipramine (25–100 nA; 20–60 seconds). (Cells were excluded if the variation between control responses exceeded $\pm$ 10%; Bradshaw *et al.*, 1974). Only excitatory responses were selected for study in these experiments.

**Results** The effect of desipramine was studied in the cat on 11 cortical neurones which responded with a clear excitation to mescaline. On 5 cells the response to mescaline was potentiated following an application of desipramine. (A response was regarded as potentiated if there was an increase of 20% or more over the size of the mean control response; Bradshaw *et al.*, 1974). On 6 cells desipramine antagonized the response to mescaline. (A response was regarded as antagonized if there was a decrease of 20% or more in the size of the response compared with the mean of the control responses; Bradshaw *et al.*, 1974). On 2 cells both antagonism and potentiation could be observed following a brief application of desipramine: the antagonism preceded the potentiation. An example of a study in which both potentiation and antagonism could be observed on the same cell is shown in Figure 1a and b.

Seventeen cortical neurones were studied in the rat.

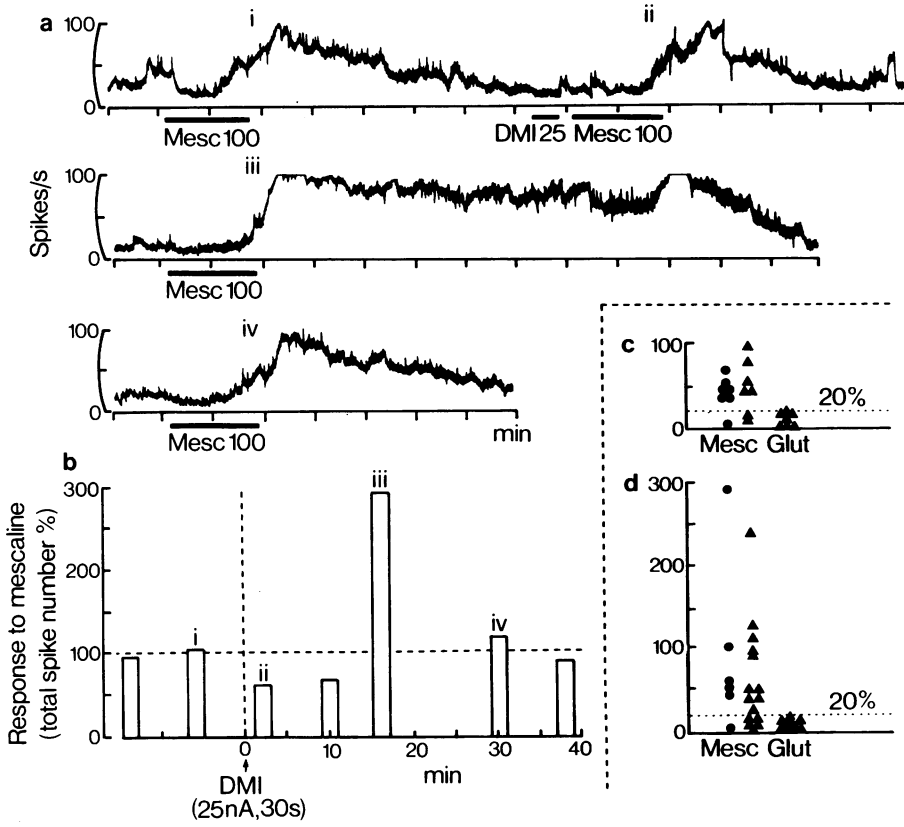


**Figure 1** (a and b) Effect of desipramine on responses to mescaline of a single neurone in cat cerebral cortex. (a) Excerpts from the ratemeter recording of the firing rate of the neurone. Horizontal bars indicate drug applications; numbers refer to the intensity of the ejecting current (nA). (b) Time-course of entire study. Height of columns indicate the total number of action potentials generated in response to each application of mescaline, expressed as % of mean control (see Bradshaw *et al.*, 1974). Numbers above columns indicate sections of the study shown in the excerpts above. Following a brief application of desipramine the response to mescaline was first antagonized and later potentiated. (c and d) Summary of results obtained on all cells. (c) Antagonism: each point shows the maximum degree of antagonism observed in one individual cell (e.g. response ii in b). (d) Potentiation: each point shows the maximum potentiation observed in one individual cell (e.g. response iii in b). Closed circles refer to results obtained in cats, closed triangles to results obtained in rats.

In these studies, glutamate was used as a control agonist. Desipramine potentiated the response to mescaline on 10 cells; on 5 of these the potentiation was preceded by antagonism of the response. Responses to glutamate were not affected by desipramine.

The maximum degrees of antagonism and potentiation seen in each cell are shown in Figure 1c and d respectively.

**Discussion** The effects of desipramine on responses to mescaline are similar to its effects on responses to noradrenaline (Bradshaw *et al.*, 1974; Bevan *et al.*, 1974). Both antagonism and potentiation of neuronal responses to mescaline could be observed. The antagonism may reflect the $\alpha$-adrenolytic action of desipramine (Callingham, 1967), since mescaline and noradrenaline probably activate similar receptors on cortical neurones (Bevan *et al.*, 1974). The potentiation of responses to mescaline is more difficult to explain: uptake mechanisms are unlikely to be involved, since desipramine does not block the uptake of mescaline into cortical synaptosomes (Bevan, 1975). An alternative possibility is that the potentiation has a post-synaptic origin: desipramine may block 'masked' inhibitory receptors on the post-synaptic membrane and thus increase the size of the observed excitatory response to mescaline (Bradshaw *et al.*, 1974; Bevan *et al.*, 1974).

This work was supported by the Scottish Home and Health Department and the Mental Health Trust and Research Fund. We are grateful to R. Lamb for technical assistance.

**References**

BEVAN, P. (1975). The uptake of mescaline by rat brain synaptosomes. *Br. J. Pharmac.*, **54**, 257–258P.

BEVAN, P., BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1974). The effect of microelectrophoretically applied mescaline on cortical neurones. *Neuropharmacology*, **13**, 1033–1045.

BEVAN, P., BRADSHAW, C.M. & SZABADI, E. (1975a). Effects of desipramine on neuronal responses to dopamine, noradrenaline, 5-hydroxytryptamine and acetylcholine in the caudate nucleus of the rat. *Br. J. Pharmac.*, **54**, 285–294.

BEVAN, P., BRADSHAW, C.M. & SZABADI, E. (1975b). Effects of iprindole on responses of single cortical and caudate neurones to monoamines and acetylcholine. *Br. J. Pharmac.*, **55**, 17–25.

BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1974). Effects of imipramine and desipramine on responses of single cortical neurones to noradrenaline and 5-hydroxytryptamine. *Br. J. Pharmac.*, **52**, 349–358.

CALLINGHAM, B.A. (1967). The effects of imipramine and related compounds on the uptake of noradrenaline into sympathetic nerve endings. In *Antidepressant Drugs, Proc. 1st Int. Symp. Milan*, ed. Garattini, S. & Dukes, M.N.G., pp. 35–43. Amsterdam: Excerpta Medica.

HORN, A.S., COYLE, J.T. & SNYDER, S.H. (1971). Catecholamine uptake by synaptosomes from rat brain. Structure activity relationships of drugs with differential effects on dopamine and norepinephrine neurones. *Mol. Pharmac.*, **7**, 66–80.

IVERSEN, L.L. (1967). *The Uptake and Storage of Noradrenaline in Sympathetic Nerves*. Cambridge: Cambridge University Press.

IVERSEN, L.L. (1974). Uptake mechanisms for neurotransmitter amines. *Biochem. Pharmac.*, **23**, 1927–1935.

ROSS, S.B., RENYI, A.L. & ÖGREN, S.-O. (1971). A comparison of the inhibiting activities of iprindole and imipramine on the uptake of 5-hydroxytryptamine and noradrenaline in brain slices. *Life Sciences*, **10**, 1267–1277.

SIGG, E.B., SOFFER, L. & GYERMEK, L. (1963). Influence of imipramine and related psychoactive agents on effects of 5-hydroxytryptamine and catecholamines on cat nictitating membrane. *J. Pharmac. exp. Ther.*, **142**, 13–20.

*(Received December 15, 1975.)*