Antagonism of catecholamine inhibition of brain stem neurones by mescaline

Mescaline (3,4,5-trimethoxyphenylethylamine) is a well-known psychomimetic agent, able to induce hallucinations and psychotic-like episodes in humans[9], and a catatonic syndrome in animals[10]. Its precise mechanism of action is not known. It has been demonstrated recently that two compounds which induce catatonia are able to antagonise the inhibitory actions of L-noradrenaline and dopamine, when applied by iontophoresis to brain stem neurones[6,7]. Since these catatonia-producing compounds have methoxy groups attached to a structure bearing some resemblance to a phenylethylamine, it was decided to investigate the trimethoxy-compound mescaline (to test whether it had a similar action).

The experiments were performed in unanaesthetized, decerebrate cats as previously described[3]. Five-barrelled microelectrodes were inserted through the floor of the IVth ventricle, after removal of the cerebellum. Extracellular neuronal spikes were recorded through a barrel containing 4 *M* NaCl via a cathode follower. The spikes were displayed on an oscilloscope, and electronically counted; a cumulative record over 5-sec epochs was displayed on a pen recorder. The drugs used were: mescaline sulphate (0.25 *M*), pH 4.5; L-noradrenaline HCl (0.5 *M*), pH 4.0; 5-hydroxytryptamine bi-maleinate (0.5 *M*), pH 4.0; acetylcholine chloride (1.0 *M*), pH 6.0; glycine (1.0 *M*), pH 3.0; γ-aminobutyric acid (GABA) (1.0 *M*), pH 3; adequate controls of the possible current effects were tested through the remaining barrel which was filled with 2 *M* NaCl. All drugs were applied with currents of appropriate polarity, in the range of 30–75 nA for periods of 30 sec, except mescaline which was applied for longer periods (3–6 min). A total of 75 neurones were studied in the brain stem in the region between 2–6 mm from obex and 0.5 –2mm from the midline. Mescaline itself affected the firing rate of 21 % of the neurones tested, exciting 12 % and inhibiting 9 % of the neurones tested. These actions were slow in onset but rarely outlasted the period of application.

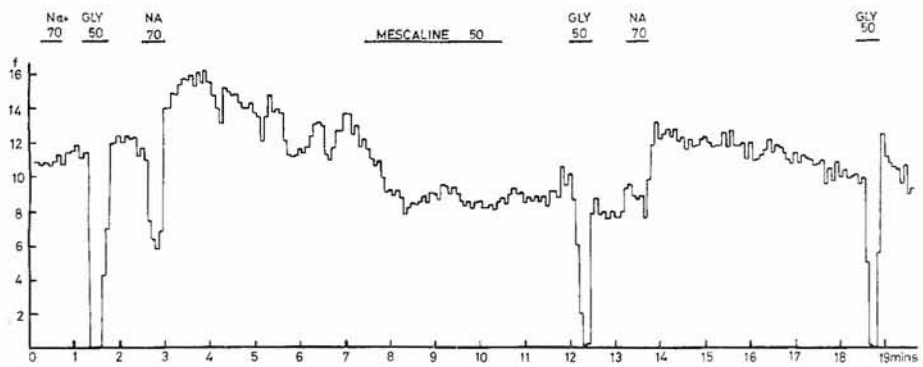

Fig. 1. Antagonism of noradrenaline inhibition by mescaline. Only the inhibitory phase was antagonised, and the inhibitory responses to glycine remain unaffected. Bars indicate length of the application, figures indicate iontophoretic current in nA. Ordinate (f) firing rate in impulses/sec. NA = L-noradrenaline; Gly = glycine; mesc = mescaline; Na^+ = sodium.

L-Noradrenaline produced characteristic responses, as described by Boakes *et al.*[2], and the actions of dopamine resembled those of noradrenaline. The application of mescaline for periods of 3–6 min antagonised inhibitory responses in 9 out of 20 neurones for L-noradrenaline, and in 11 out of 14 for dopamine, and both short and long lasting types of inhibition were antagonised. This antagonism developed after a latent period of about 3–15 min after the end of the application of mescaline and lasted in some cases for more than 15 min. In neurones showing biphasic responses to L-noradrenaline and dopamine (short inhibition followed by excitation) only the inhibitory phase was antagonised. The antagonism produced by mescaline was not related to the reduction in firing level which occasionally followed the application of this drug. Thus antagonism was observed without any appreciable change in firing level (Fig. 1), and it was regularly observed that the presence or absence of inhibition by noradrenaline or dopamine was not related to the firing levels (Fig. 2). Mescaline failed to antagonise excitatory responses to L-noradrenaline and dopamine as well as responses to 5-hydroxytryptamine (5-HT) (Fig. 3), acetylcholine, glycine and GABA tested in the same fashion (Table I).

TABLE I

ACTION OF MESCALINE IN RELATION TO OTHER COMPOUNDS

		Number of neurones	*Number of responses antagonised by mescaline*
NA	—	20	9
	+	11	0
DA	—	14	11
	+	7	0
5-HT	—	5	0
	+	8	0
ACh	+	8	0
Gly	—	12	0
GABA	—	5	0

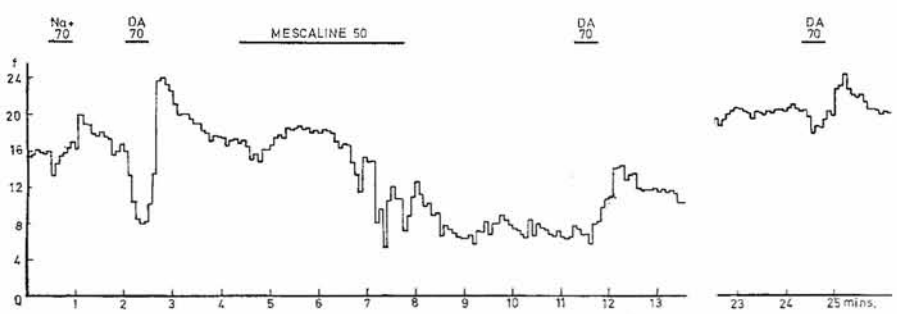

Fig. 2. Complete block of the dopamine inhibition was present 3 min after the end of the mescaline application. Antagonism was still almost complete 13 min later at a firing level similar to that prior to the mescaline application. DA = dopamine.

The present results agree with previous findings on the mode of action of catatonia-inducing methoxy compounds[6,7]. However, they differ from the results of Roberts and Straughan[11] who did not find any antagonism of mescaline on cortical responses to L-noradrenaline. This could have been due to a difference between cortical and brain stem receptors for catecholamines, which has become evident from a comparison of the effects of agonists and antagonists in these two regions[2,8].

It has been suggested that mescaline acts via the formation of an intermediate metabolite or through the formation of an LSD-like compound (for review see Giarman and Freedman[5]), and the long latency before its antagonistic action develops would support this possibility, although it does not seem probable that an LSD-like compound is involved in view of its failure to antagonise 5-HT actions[1]. Although peripheral and central adrenergic receptors appear to be different in some respects[2] it is interesting to note that agonistic and antagonistic actions of mescaline on α adrenergic receptors have been described[4].

The relevance of these observations to an explanation of the effects produced by the systemic administration of mescaline remains to be evaluated. However, it can be suggested that the production of catatonia by mescaline might well be related to the effects described in these experiments since 3 other compounds which have been tested recently, 3,4-dimethoxyphenylethylamine[6], bulbocapnine[7] and papaverine (Gonzalez-Vegas, unpublished results) also antagonise the inhibitory actions of L-noradrenaline and dopamine and produce catatonia.

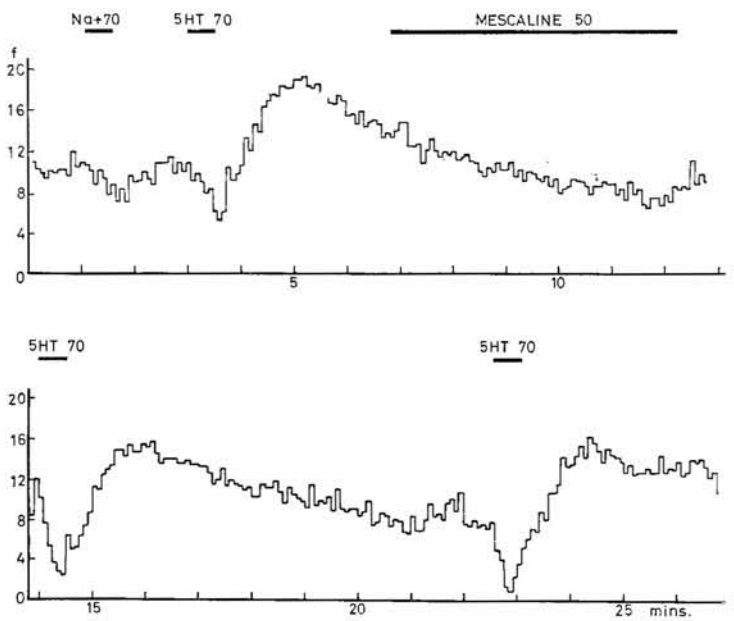

Fig. 3. Lack of effect of iontophoretically applied mescaline in relation to 5-HT inhibitory and excitatory responses.

J. A. G.-V. holds a Universidad Central de Venezuela Scholarship.

This work was supported by grants from the Universidad Central de Venezuela and from the Medical Research Council to Professor J. H. Wolstencroft.

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(Accepted September 15th, 1971)