Short communications

Effect of mescaline on single cortical neurones

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The effects of mescaline upon single cortical neurones were studied, using the microiontophoretic technique. Mescaline elicited excitatory and depressant responses similar to those evoked by noradrenaline (NA) and 5-hydroxytryptamine (5-HT). The responses to NA and mescaline were usually in the same direction, the neurone being either excited by both drugs or depressed by both drugs. The correlation between the effects of mescaline and 5-HT, however, was less consistent. The β-adrenoceptor blocking agent MJ-1999 and the 5-HT antagonist methysergide were both effective in antagonizing mescaline responses.

The hallucinogen, lysergic acid diethylamide (LSD25), antagonizes the actions of 5-hydroxytryptamine (5-HT) on various peripheral systems, and this action has recently been observed on single neurones of the cerebral cortex (Roberts & Straughan, 1967) and the brain stem (Boakes, Bradley, Briggs & Dray, 1970). We wish to report some studies of the effects of another hallucinogen, mescaline (3, 4, 5-trimethoxyphenylethylamine) upon single cortical neurones.

Little information is available about the effects of iontophoretically applied mescaline upon single neurones, and even this is contradictory. Iontophoretically applied mescaline had only a feeble depressant action on single neurones of the lateral geniculate nucleus (Curtis & Davis, 1962) and the cerebral cortex (Krnjević & Phillis, 1963). More recently, however, an excitatory action of mescaline on cortical neurones has been observed (Roberts & Straughan, 1968). This study consists of an investigation of the agonistic action of mescaline, and of the actions of antagonists of noradrenaline (NA) and 5-HT upon the mescaline response. The basis of the latter study is the observation of Roberts & Straughan (1967) and Johnson, Roberts, Sobieszek & Straughan (1969) that there are separate excitatory receptors for 5-HT and NA on cortical neurones which can be affected by conventional 5-HT and NA antagonists.

Methods.—Experiments were carried out on cats of either sex anaesthetized with halothane (0·5–1·5%). Spontaneous activity of single cells of the somatosensory cortex was recorded via one barrel of a five barrelled glass micropipette with a tip diameter of 3–6 μm. The recording barrel was filled with 3 M NaCl, as was a second barrel, which was used to examine the effects of current upon the cell. The other three barrels contained drug solutions. Our techniques for preparing the animals, and for studying single units, have been described elsewhere (Roberts & Straughan, 1967; Johnson, Roberts, Sobieszek & Straughan, 1969). The following drugs were used in these experiments: mescaline hydrochloride (0·2 M, pH 3·5), noradrenaline bitartrate (0·2 M, pH 3·5), 5-hydroxytryptamine bimaleate (0·2 M, pH 3·5), acetylcholine chloride (0·2 M, pH 4·0), MJ-1999, sotalol (4-(2-isopropylamino - 1 - hydroxyethyl) - methanesulfonanilide hydrochloride) (0·1 M, pH 4·0), methysergide bimaleate (0·01 M, pH 3·5).

Results.—Mescaline had either an excitatory or a depressant action on the firing rate of cortical neurones: of 142 cells responsive to mescaline, 112 (79%) were excited and thirty (21%) were depressed by the drug. The iontophoretic currents and the duration of application required to obtain these responses fell within the same range as those used to evoke responses to NA and 5-HT (50–100 nA for 30–60 s). The latency, duration and amplitude of the mescaline responses resemble those of the NA and 5-HT responses more closely than they resemble responses to ACh and glutamate.

We compared the direction of the responses (excitation or depression) of individual neurones to NA and 5-HT. There was a certain lack of correlation between the directions of the responses: of thirty-four cells, seven (20·5%) responded in opposite directions to NA and 5-HT. Mescaline also was applied to these seven cells, and in every case the mescaline response resembled the NA rather than the 5-HT response. When the responses of

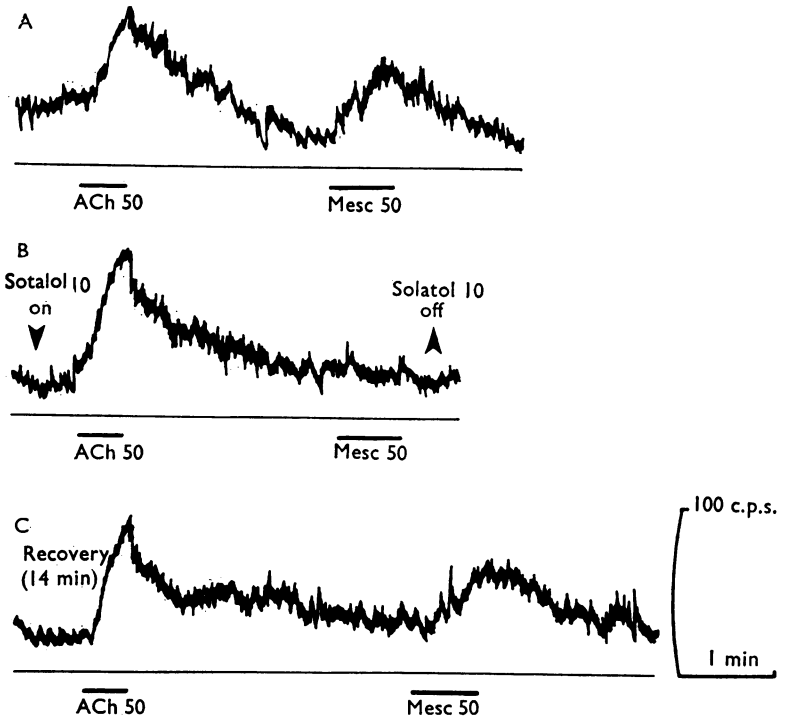

FIG. 1. Excerpts from a ratemeter tracing of the firing rate of a single cortical neurone. Full scale deflection of the pen from the baseline represents a firing rate of 100 spikes/s; the time calibration is one minute. The durations of the drug applications are represented by horizontal bars; numbers refer to iontophoretic current in nA. A, The excitatory responses to ACh and mescaline (Mesc.) before the application of sotalol. B, Complete blockade of the mescaline response, but no change in the ACh response during the continuous application of sotalol. C, Complete recovery of the mescaline response 14 min later.

individual neurones to mescaline and NA were compared, only one neurone (<1%) out of a total of 126 responded in opposite directions to the two drugs. However, of fifty neurones studied with mescaline and 5-HT, nine (18%) yielded opposite responses to the two drugs.

We have also examined the actions of the β-adrenoceptor blocking agent, sotalol (MJ-1999), and the 5-HT antagonist methysergide, upon the mescaline response. Sotalol antagonized the excitatory actions of mescaline. The actions of the antagonist upon the NA and mescaline responses were compared on some cells: the mescaline and NA responses were antagonized with similar time courses, and recovery proceeded in the same way for both drugs. In order to assess the specificity of the antagonism of the mescaline response, acetylcholine (ACh) was used as a control agonist on several cells. One of these is shown in Fig. 1. The application of sotalol with a small iontophoretic current abolished the mescaline response, while the ACh response was unaffected. After the application of the antagonist had been terminated, complete recovery of the mescaline response was observed.

The 5-HT antagonist, methysergide, is also effective in blocking the mescaline response at iontophoretic currents which do not affect the ACh response. 5-HT and mescaline responses of the same cells were antagonized by methysergide to a similar degree and with similar time courses.

Discussion.—We have confirmed that mescaline can excite or depress cortical neurones. These actions of mescaline strongly resemble the excitatory and depressant actions of NA and 5-HT, which are quite different from the excitatory actions of ACh and glutamate (Johnson, Roberts, Sobieszek & Straughan, 1969), and the depressant actions of glycine and

GABA (Johnson, Roberts & Straughan, 1970).

The agonistic effects of mescaline are in contrast with the effects of the indolethylamine hallucinogen, LSD25, which has only a weak, prolonged depressant action upon cortical neurones (Roberts & Straughan, 1967). The most remarkable pharmacological action of LSD25 on cortical neurones is the antagonism of 5-HT responses, and it is, therefore, of interest to know whether mescaline has an antagonistic action on 5-HT or NA responses. Roberts & Straughan (1968) reported that long applications of mescaline (up to 10 min) failed to antagonize NA responses. 5-HT responses do not appear to be grossly affected by prior application of mescaline, but the study of interaction between mescaline and 5-HT is not yet complete.

The resemblance of the mescaline responses to both NA and 5-HT responses suggested that mescaline might act upon the NA or the 5-HT receptor. In an attempt to identify the receptor involved, we performed the correlation studies. When NA and 5-HT were applied to the same neurones, 20·5% (seven out of 34) of the cells responded in opposite directions. When NA was replaced by mescaline, and both mescaline and 5-HT were applied to the same neurones, a similar proportion, 18% (nine out of 50) responded in opposite directions to the two drugs. These findings suggested that mescaline might act primarily on the NA receptor. This suggestion gained further support from the very strong correlation (>99%) between the NA and mescaline responses. Cells which responded in opposite directions to NA and mescaline were observed by Roberts & Straughan (1968); our observations suggest that such cells are very rare.

Our observations with the NA antagonist, sotalol, are also consistent with the hypothesis that mescaline acts on NA receptors. However, the 5-HT antagonist, methysergide, was also capable of antagonizing mescaline responses. We are, at present, comparing the actions of methysergide upon the mescaline, NA and 5-HT responses of the same cells in order to investigate the specificity of these interactions more closely, since it has not yet been demonstrated that methysergide can discriminate between the actions of NA and 5-HT on single cortical neurones.

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