

TABLE 1. Increased efflux of GABA from cat cerebral cortex in response to electrical stimulation in the presence and absence of calcium.

| Nature of inhibitory stimulation           | Increase in GABA efflux<br>(Mean $\pm$ S.E.M.) |   |
|--|--|---|
| Cortex (monopolar)                         | 3.72 $\pm$ 0.085 ( $n=9$ , $P<0.02$ )          |   |
| Cortex (bipolar)                           | 8.58 $\pm$ 1.679 ( $n=13$ , $P<0.0005$ )       |   |
| LGN  | 5.45 $\pm$ 1.491 ( $n=6$ , $P<0.02$ )          |   |
| Cortex (bipolar, Ca <sup>++</sup> present) | 6.98 $\pm$ 0.918 ( $n=5$ )                     | Significantly<br>different<br>( $P<0.002$ ) |
| Cortex (bipolar, Ca <sup>++</sup> absent)  | 1.46 $\pm$ 0.298 ( $n=5$ )                     |   |

Results are expressed as ratios of the resting efflux of GABA in samples collected immediately before stimulation.  $n$  = number of experiments.

The resting efflux of endogenous GABA remained steady during the course of each experiment (mean of sixteen experiments,  $0.19 \pm 0.028$  nmol/7 min). Electrical stimulation of the cortical surface or the lateral geniculate nucleus (LGN) produced cortical inhibition and evoked significant increases in the output of GABA (Table 1). Increases in the efflux of <sup>3</sup>H-GABA similar to those described previously (Mitchell & Srinivasan, 1969) were obtained during stimulation. The average output of ninhydrin-positive material was  $0.22 \pm 0.034$   $\mu$ mol/7 min and this was not significantly altered by electrical stimulation.

These results show a calcium-dependent release of endogenous GABA from the cortex during synaptic inhibition, and thus provide further evidence that GABA is a transmitter at certain inhibitory synapses in the mammalian cerebral cortex.

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#### Effects of lysergic acid derivatives on 5-hydroxytryptamine excitation of brain stem neurones.

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The suggestion by Woolley & Shaw (1954) that a central antagonism to 5-hydroxytryptamine (5-HT) might explain the psychotomimetic effects of (+)-lysergic acid diethylamide (LSD 25) has been followed by a number of attempts to demonstrate such an action. Where an antagonism has been shown, other peripheral 5-HT antagonists which have little or no psychotomimetic properties have often been found to be effective. Bradley & Wolstencroft (1965) reported that 5-HT applied iontophoretically has excitatory and inhibitory actions on single neurones in the brain stem of the decerebrate cat. Using the same technique and preparation, we have studied the interactions of LSD 25, 2-bromo-lysergic acid diethylamide (BOL) and methysergide with these effects of 5-HT and of other compounds which stimulate or depress neuronal activity.

LSD 25, applied iontophoretically for periods of 5 min or more at currents of 50 nA, consistently blocked or depressed excitatory responses to 5-HT but not those to acetylcholine, (-)-noradrenaline or ( $\pm$ )-homocysteic acid. LSD 25 did antagonize

the excitatory effects of glutamate ions on neurones which could be excited by 5-HT, but not on neurones which could be inhibited by 5-HT. Inhibitory responses to 5-HT, acetylcholine, (—)-noradrenaline, glycine and  $\gamma$ -aminobutyrate were never affected by LSD 25.

BOL, applied in the same way as LSD 25, only rarely showed antagonism to 5-HT excitation and to glutamate excitation of neurones which could be excited by 5-HT. BOL did not affect 5-HT inhibition, glutamate excitation of neurones which could be inhibited by 5-HT, or the excitatory or inhibitory actions of other compounds tested.

Methysergide antagonized 5-HT and glutamate excitation more frequently than BOL, but less frequently than LSD 25. However, there was less correlation between blockade of 5-HT excitation and of glutamate excitation by this compound than between blockade of 5-HT and glutamate excitation by LSD 25.

LSD 25 therefore appears to be an effective antagonist of 5-HT excitation of neurones in the cat brain stem. Of the two analogues of LSD 25 tested, BOL, which was relatively ineffective, is not known to possess any psychotomimetic activity, whilst methysergide, which had some activity in these experiments, has been reported to be hallucinogenic (Abramson & Rolo, 1967). Thus there appears to be a tentative correlation between hallucinogenic activity and antagonism to 5-HT excitation in the brain stem.

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#### Some biochemical correlates of convulsive activity in rats.

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Although there are similarities in the nature of convulsions induced in rodents by different chemical and physical stimuli, the time and intensity of each phase of the seizure often differs. In convulsions induced by electroshock, leptazol and high intensity sound, for example, the full tonic phase of the seizure is similar and of approximately the same duration although the time of onset and the nature of the preceding behavioural changes differ. It was of interest therefore to compare some biochemical changes which occur during seizures induced by different stimuli in an attempt to determine whether the changes were a consequence of the specific nature of the seizure stimulus or merely a reflection of the convulsive activity independent of the means whereby it was initiated.

Rats were killed following electro-convulsive shock, leptazol or high intensity sound either by decapitation, for the determination of enzyme activities, or by total immersion in liquid nitrogen for the determination of labile compounds in brain. Irrespective of the nature of the seizure stimulus, a rise occurred in brain lactate (c. 160%) and ammonia (c. 200%) and a fall occurred in brain glucose (c. 70%), ATP (c. 24%), and creatine phosphate (c. 30%). Glucose-6-phosphate (c. 60%) and