Effect of cholinergic drugs on the somatosensory evoked potentials

Cortical application of acetylcholine or eserine to the exposed cerebral cortex increases the amplitude of the repetitive after-discharges of the contralateral somatosensory evoked potentials of the rat anaesthetized with pentobarbitone (Bhargava, 1969). These drugs do not produce any effect on the primary complex (short latency positive-negative waves) of the somatosensory evoked potentials. It was suggested that the afferent pathways responsible for the primary complex of the cortical evoked potentials are not cholinergic, whereas those responsible for the repetitive after-discharges following an afferent volley, are cholinergic. The present paper reports the effect of acetylcholine on the somatosensory evoked potentials on prior eserinization of the cortex, to further strengthen this hypothesis.

Male albino rats of CFE strain (Sprague Dawley from Carworth, Europe), 250–300 g, were anaesthetized with pentobarbitone (50 mg/kg initially, then 12 mg/kg half hourly) intraperitoneally.

Computer derived averages of thirty-two consecutive somatosensory evoked potentials from both cortices in response to the ipsilateral and the contralateral stimulation of the forepaws were recorded (Bhargava & Meldrum, 1969). Drugs dissolved in artificial cerebrospinal fluid (CSF) (Bradbury & Davson, 1964) were applied on the somatosensory area through the specially designed cortical cups mounted on the exposed cortices. Manually, the drugs were applied to one cortex while the other cortex was bathed with normal CSF and served as control during the experimental period.

In each experiment 10^{-5} or 10^{-3}M eserine was applied to one cortex for 30 min, and thereafter 10^{-3}M acetylcholine was applied on the same cortex (eserinized) for 15 min.

Cortical application of acetylcholine after prior treatment of the cortex with eserine did not produce any significant effect on the amplitude of the positive and the negative waves of the primary evoked potentials. However, in all experiments, application of 10^{-5}M eserine for 30 min produced an increase in the amplitude of the repetitive after-discharges, which were further augmented when the eserinised cortex was treated with acetylcholine (10^{-3}M). On average, the amplitude of the repetitive after-discharges after 10^{-3}M acetylcholine was 172 ± 82 μV following eserinization of the cortex ($n = 10$), and 75 ± 7 μV in non-eserinized cortex ($n = 15$). In some experiments the augmentation of the repetitive after-discharges was more marked after 5–10 min of washing off the drug, this was often seen when 10^{-3}M eserine and 10^{-3}M acetylcholine was used. The effect of these concentrations of eserine and acetylcholine on the amplitude of the repetitive after-discharges was also less marked.

Fig. 1 shows a typical experiment of this series. 10^{-5}M eserine was applied to one cortex for 30 min, followed by 10^{-3}M acetylcholine for 15 min on the same cortex. Eserine on its own increased the amplitude of the repetitive after-discharges in 20–30 min, which were further augmented 8–12 min after application of 10^{-3}M acetylcholine. The effect on the primary evoked potentials was not significant. Both positive and negative waves were slightly increased after eserine, but were not affected after application of acetylcholine, whereas the amplitudes of the repetitive after-discharges were augmented.

In the control (non-drug treated) hemisphere, cortical potentials following ipsilateral and contralateral stimulation of the forepaws were not affected when eserine and acetylcholine were applied on the other cortex.

Cortical evoked potentials following stimulation of the ipsilateral forepaw also remained constant on both cortices in all experiments.

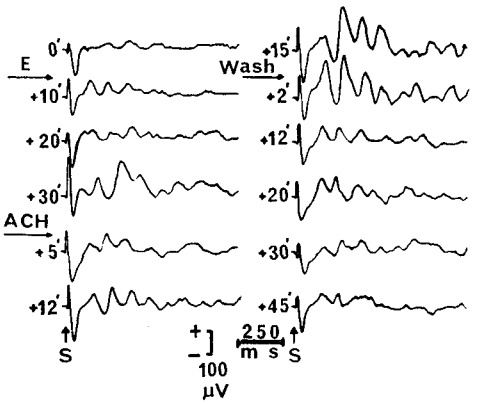


FIG. 1. Each trace is the average of thirty-two consecutive responses recorded during a 1 s epoch following stimulation of the contralateral forepaw. Positivity at the surface of the primary receiving area is shown upwards. Eserine (10^{-5}M) was applied to the right cortex for 30 min followed by acetylcholine (10^{-3}M) to the same cortex for 15 min. Note: that eserine (10^{-5}M) itself increased the amplitude of the repetitive after-discharges, which were further augmented after application of acetylcholine to the same cortex. Calibration 100 μV. Time base 250 ms.

The accumulated evidence presented above is consistent with the existence of functionally significant cholinergic synapses in the cerebral cortex. The somatosensory evoked potentials following an afferent volley from a peripheral nerve consist of an initial positivity and a late negativity of the primary receiving area (Adrian, 1941; Marshall, 1941; Amassian, 1952). The primary evoked response represents the sequence of events in cortex following an afferent volley, the positive and negative waves represent depolarization of the pyramidal cells and the apical dendrites respectively (Bhargava & Meldrum, 1969). The primary evoked potential is followed by a series of positive–negative waves called repetitive after-discharges. These waves occur at a frequency of 6–10/s and arise as a result of successive post synaptic excitatory and inhibitory potentials. The present study supports the view (Bhargava, 1969) that afferent pathways responsible for the primary evoked potentials are not cholinergic, whereas those responsible for the repetitive after-discharges are cholinergic. The repetitive after-discharges following an afferent volley are augmented after cortical application of cholinomimetic drugs, while the primary complex of the somatosensory evoked potentials remains unaffected after such treatment. This effect was best obtained when smaller concentrations of eserine (10^{-5}M) and acetylcholine (10^{-3}M) were employed. A lesser effect was seen with higher concentrations of eserine. This may be due to accumulation of an excessive amount of acetylcholine, resulting in continuous, random firing of cholinoceptive units which may preclude the generation of evoked potentials, or as a result of persistent depolarization of cholinoceptive units due to excessive acetylcholine.

The present study thus also provides electrophysiological evidence for the presence of cholinergic thalamo-cortical pathways, responsible for the augmenting and repetitive after-discharges, as shown by Collier & Mitchell (1966–67), on the basis of their studies on the spontaneous and the evoked release of acetylcholine from the surface of the brain.

Medical Research Council Neuropsychiatry Unit,
Carshalton, Surrey, U.K.

V. K. BHARGAVA*

September 1, 1970

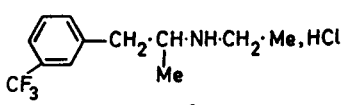
* Present address: Department of Pharmacology, Maulana Azad Medical College, New Delhi, India.

REFERENCES

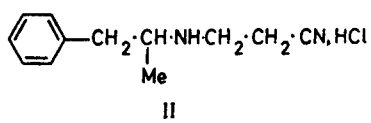
ADRIAN, E. D. (1941). *J. Physiol., Lond.*, **100**, 159–191.
AMMASSIAN, V. E. (1952). *Res. Publs Ass. Res. nerv. ment. Dis.*, **30**, 371–402.
BHARGAVA, V. K. (1969). Ph.D. Thesis Council for National Academic Awards, London.
BHARGAVA, V. K. & MELDRUM, B. S. (1969). *Br. J. Pharmac.*, **37**, 112–122.
BRADBURY, M. W. B. & DAVSON, H. (1964). *J. Physiol., Lond.*, **170**, 195–211.
COLLIER, B. & MITCHELL, J. F. (1966). *Ibid.*, **185**, 22–23*P*.
COLLIER, B. & MITCHELL, J. F. (1967). *Ibid.*, **188**, 83–98.
MARSHALL, W. H. (1941). *J. Neurophysiol.*, **4**, 25–43.

Inhibition by appetite suppressants of the pressor response to (+)-amphetamine in anaesthetized cats

Recently Jespersen & Bonaccorsi (1969a) reported an anti-amphetamine activity of fenfluramine (I) in the isolated tail artery of the rat. These authors observed that the constrictor response to tetrabenazine in the presence of amphetamine was inhibited by fenfluramine in this preparation. At the time of publication we were investigating the effects of another appetite suppressant, fenproporex (II), on the cardiovascular system of the anaesthetized cat where we found that after intravenous administration of fenproporex, (+)-amphetamine failed to produce a substantial pressor response. As a result of this observation we made further experiments which included studies of the effects of both fenproporex and fenfluramine on the pressor responses to tyramine as well as (+)-amphetamine. Cats anaesthetized with sodium pentobarbitone were used and all agents were injected intravenously.



I



II

Fenproporex was shown to have no pressor activity and relatively large doses (3–10 mg/kg) caused marked but transient reductions in blood pressure. When (+)-amphetamine, 0·01–0·1 mg/kg, was administered after a 10 mg/kg dose of fenproporex little or no rise in blood pressure resulted. These doses of (+)-amphetamine produced pressor responses in cats that received no fenproporex, or when given before fenproporex (Fig. 1A). Increasing the dose of (+)-amphetamine did not overcome the inhibitory effect of fenproporex, in fact larger doses (1–10 mg/kg) in the presence of fenproporex caused dose-dependent reductions in blood pressure (see also Fig. 1A). In further experiments, a dose of (+)-amphetamine to produce a marked pressor response (usually 0·03–0·1 mg/kg) was administered before and after various doses of fenproporex. We observed that whereas a 1 mg/kg dose of fenproporex caused only a slight reduction of the (+)-amphetamine pressor response, a 3 mg/kg dose usually caused complete inhibition. At this stage, larger doses of (+)-amphetamine again produced depressor responses.

When the above experiments were repeated using tyramine instead of (+)-amphetamine, no inhibition by fenproporex of the pressor responses to tyramine was observed (Fig. 1B) and in some instances the tyramine response was potentiated. Subsequent doses of (+)-amphetamine (0·1–5 mg/kg) failed to elicit pressor responses, the blood pressure being either unaffected or reduced according to the dose.