THE EFFECT OF AMPHETAMINE ON THE POTENTIALS EVOKED IN THE RETICULAR FORMATION

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SUMMARY

Auditory evoked responses were studied in the mesencephalic reticular formation of the encephale isole preparation of the cat. The response was complex in nature and consisted of an initial fast potential followed by a slower potential. The effects of dl-amphetamine were studied on the amplitude of the complex response. dl-Amphetamine administered intravenously in low doses significantly increased the amplitude of the slow component of the potential while large doses decreased the amplitude. The results thus obtained lend support to the fact that low doses of amphetamine can increase the level of attention and vigilance while large doses can decrease attention.

INTRODUCTION

The previous report of Morruzi and Magoun (1949) indicated that the responses recorded in the reticular formation consisted of slow potentials. However, De Maar and his co-workers (1958) reported two types of evoked potentials recorded in the brain stem reticular formation in response to sciatic nerve stimulation in the cat. Recently, Grillo (1977) reported two types of evoked potentials, consisting of 'fast' and 'slow' components, in response to auditory stimulus in an encephale isole preparation of the cat. It was reported earlier (Grillo, 1968) that the slow component was concerned with part of the mechanisms responsible for attention and integration of sensory information. Studies were therefore conducted to find the effects of small and large doses of amphetamine on the slow components of the potentials recorded in the mesencephalic reticular formation of the brain stem.

METHODS

Acute experiments were performed on unanesthetized encephale isole preparations of cats. A total of 13 adult cats of either sex and weighing between 1.75 and 2.5kg were used. Initially, anaesthesia was induced with ethyl chloride and then maintained with ether. After tracheotomy, the head of the animal was fixed in position with a stereotaxic apparatus (La Presicion Cinematographique, France). A spinal section at the first cervical level was quickly performed using the method previously described by Bradley and Key (1958) and the animal was immediately placed on artificial respiration maintained with a Palmer respiratory pump. Next, the position of the primary auditory area was marked on the skull and small burr holes were drilled for the insertion of three cortical electrodes. Similarly three other holes were made for electrodes to be inserted over the mid-ectosylvian, lateral, and middle supra - sylvian gyri. The dura underneath each hole was carefully pierced with a needle and the six cortical electrodes were screwed into place on the same side of the skull. The tip of each electrode just rested on the cortex. An earthing electrode was placed in the mid-line over the frontal sinus, while the femoral vein was exposed and cannulated for the administration of drug. After all the operative procedures had been completed the wound margins and pressure points were infiltrated with 1% lidocaine solution. Ether anaesthesia was then discontinued and at least 1 hour was allowed to elapse before the experiment was started. Subsequent repeated injections of the local anaesthetic around the wound edges and pressure points were given during the experiment. Throughout all of these experiments there was no indication that the animal was in pain or discomfort.

The cortical electrodes used were prepared according to the method of Bradley and Elkes (1953). The general procedure for locating and recording potentials evoked in the mesencephalic reticular formation and the primary auditory cortex in response to click stimuli presented monoaurally to the experimental animals was as follows. A bipolar concentric electrode was inserted stereotaxically into the mesencephalic reticular formation according to Horsley - Clarke co-ordinates (A.2.0., L.2.0. and H.O to -2). The electrode was inserted into the reticular formation gradually at 1 mm steps. The electrode placement was contralateral to the side from which cortical recordings were taken. Using only the inner conductor of the bipolar electrode, monopolar recordings were made with reference to an electrode attached to one of the arms of the stereotaxic instrument. Electrical activity from the cortical and subcortical electrodes was monitored on an eight-channel Schwarzer electroencephalograph.

The auditory stimuli presented to the animal consisted of clicks delivered by a deaf aid ear-piece attached to one of the hollow ear-bars of the stereotaxic instrument. The stimulus was thus monoaural and contralateral to the electrode placement. Each click stimulus consisted of 6 V square wave pulses of 0.5 ms duration at a frequency of 1 per 5 s. They were generated by a "Devices" 90V isolated stimulator which in turn was triggered by a "Devices" Digitimer. All of the potentials evoked in the mesencephalic reticular formation and the auditory cortex were recorded on the electroencephalograph at a paper speed of 16 mm/s.

The position of the deep electrode placement in each experiment was histologically varified. At the end of every experiment, the brain was removed and fixed in a solution of formalin and saline for at least one week; indentation marks were usually visible on the cortex. Blocks of brain tissue containing the indentation marks of the electrode were cut parallel to the Horsley-Clarke planes. The blocks were then mounted on a freezing microtome and sectioned at 100 u. The sections containing the electrode tracts were then mounted on slides and stained with thionine.

RESULT

Potentials evoked in the mesencephalic reticular formation in response to click stimuli

Experiments were performed in five cats to record simultaneously the responses evoked by clicks in the mesencephalic reticular formation and the primary auditory cortex.

The responses recorded in the mesencephalic reticular formation were complex in form and considerable variation was observed from one preparation to another and even in the same preparation. This result has been previously reported (Grillo, 1981). A typical evoked potential recorded in the mesencephalic reticular formation of the cat in response to click stimulus is shown in figure1. Recordings were made in alert encephale isole preparations of the cat. The complex response consisted of an initial fast potential of a short duration followed by a slower potential of a longer duration. The different waves of the response are numbered 1 – 5 in figure 1. The initial fast component was made up of waves 1 – 3 while the slower component was made up of waves 4 and 5.

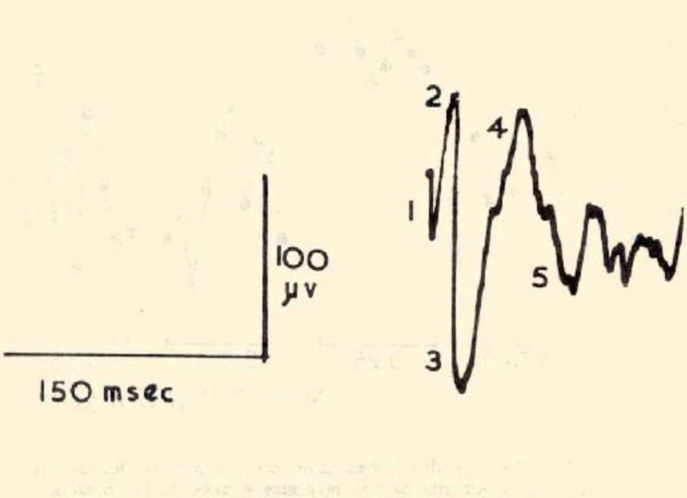

Figure 1. Evoked potential in response to click, recorded in the mesencephalic reti~lar formation of the cat encephale isole preparation. different waves are numbered 1 to 5.

The effect of dl-amphetamine on the potentials evoked in the mesencephalic reticular formation

dl – amphetamine sulphate in incremental doses of 0.25 mg/kg to a total dose of 1.75 mg/kg was administered intravenously to eight alert encephale isole preparations. Recordings were taken fifteen minutes after the administration of each dose. All the three doses of amphetamine, 0.25, 0.75 and 1.75 mg/kg injected produced a continuous desynchronization of the electrocorticogram in all the preparations.

In seven experiements 0.25 mg/kg produced a consistent increase of 20 – 35% (Fig 2) in the amplitude of the slow component of the responses evoked in the mesencephalic reticular formation. When a total dose of 0.75 mg/kg was injected the amplitude of this component was now reduced and in five of the seven experiments a significant reduction of 12–16% below the control level was observed. In the other two experiments the amplitude was reduced to near the control level. No further significant change was obtained when a total dose of 1.75 mg/kg was injected. In the eighth experiement amphetamine failed to produce any effect on the amplitude of the slow component.

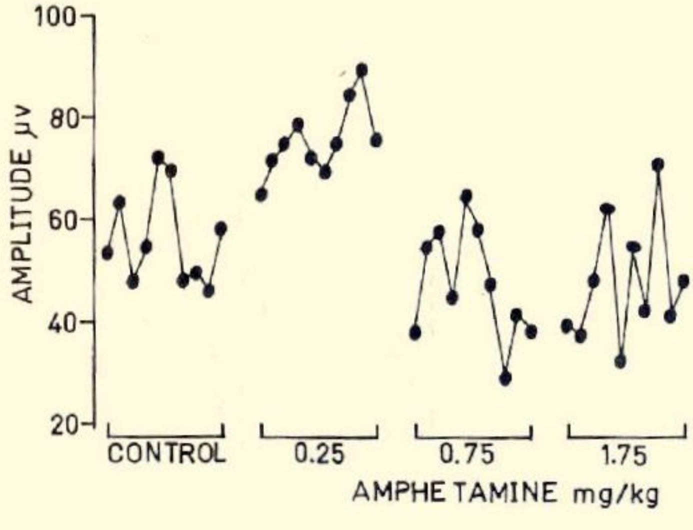

Figure 2. The effect of dl-amphetamine on the amplitudes of the slow components of the response evoked in the mesencephalic reticular formation. In this and subsequent graph of this type, each point represents the amplitude of a single evoked potential and those joined by a continuous line are successive responses.

In all the experiments the first dose of amphetamine, 0.25 mg/kg, did not produce any change in the amplitude of the initial fast component of the response evoked in the mesencephalic reticular formation (Fig 3). A decrease of 18–24% in the amplitude of the component was observed after the dose was increased to 0.75 mg/kg and no further change was seen after a total dose of 1.75 mg/kg had been administered to a preparation.

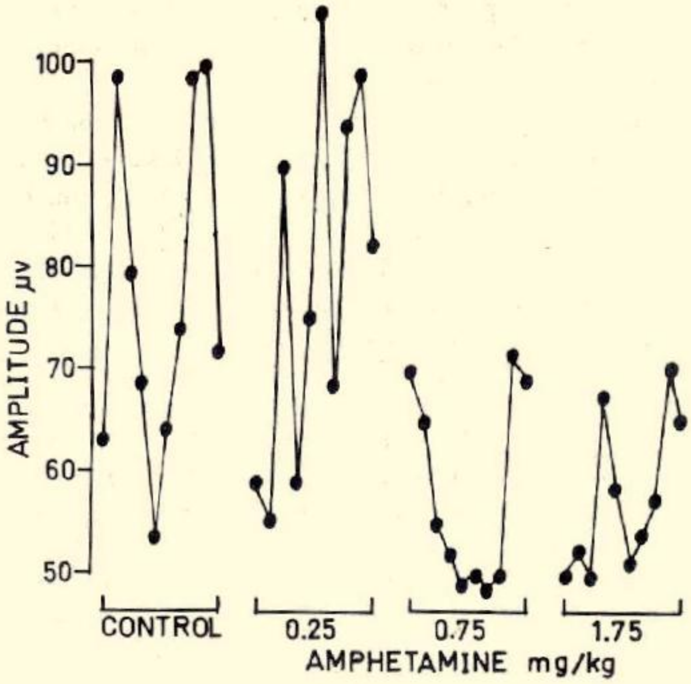

Figure 3. The effect of dl-amphetamine on the amplitudes of the fast components of the response evoked in the mesencephalic reticular formation.

DISCUSSION

The purpose of the present studies is to investigate the effect of amphetamine on attention, and for this purpose the reticular formation of the midbrain has been selected in the investigation. The anatomy and physiology of the reticular formation had been reviewed by various authors (French, 1960; Rossi and Lanchetti, 1957; Bradal, 1957; Segundo 1956;) Though this structure had been regarded as diffuse and unspecific in character, three physiological roles have been assigned to it (French 1960) The reticular formation has been implicated in the arousal response and wakefulness, the reticular formation exerts a critical degree of influence over motor functions which are concerned in the phasic and tonic muscular control, and the reticular formation is capable of modifying the reception, conduction and integration of all sensory stimuli entering the brain. It is this last physiological role of the reticular formation that is being utilized in the present studies to investigate the effect of amphetamine on attention.

It is now clear that two potentials, an initial fast potential, followed by a slower potential, can be recorded from the mesencephalic reticular formation (Demeer et al, 1958; Grillo, 1967; 1977). The slow potential was studied under three behavioural states: awake, drowsiness, and sleep (Grillo, 1967). During awakeness, the amplitude of the slow component was found to be appreciably increased when compared with those recorded during the states of drowsiness and sleep. Furthermore, an earlier report by Grillo (1967) showed that the slow component was concerned with part of the mechanism responsible for attention and integration of sensory information with regard to its significance. It is this slow potential that is used in the evaluation of the results obtained in the present investigation.

The administration of amphetamine induced the desynchronization of the electrocorticogram in the present studies. This result was in accordance with that of Bradley and Elkes (1958) who presented evidence of a direct action of amphetamine on the reticular formation. Thus lesion of the ***mid brain*** which interrupted the reticular formation pathway to the cortex caused the failure of amphetamine to activate the electrocorticogram. On the other hand, high spinal section, leaving the mesencephalon intact did not prevent the activation of the electrocorticogram.

In the present studies, the intravenous administration of 0.25 mg/kg of amphetamine produced an increase in the amplitude of the slow component of the potential recorded in the mesencephalic reticular formation. As the dose of amphetamine was increased up to 0.75 mg/kg, a decrease in the amplitude was observed. Now, according to Bremer's hypothesis (1960), since amphetamine produced desynchronization of the electrocorticogram, a decrease in the amplitude of evoked responses will be expected. The desynchronization produced by amphetamine was extended to the reticular formation in the present studies. However, a substantial increase in the amplitude of the slow component of the mesencephalic reticular formation responses was observed. There is no doubt that higher doses of the drug produced depression of the brain activity.

Thus the main effect of amphetamine was observed on the slow component of the mesencephalic reticular formation responses. This is interesting, for it has been suggested that the slow component might be part of the electrical manifestation of the mechanisms responsible for the state of attentiveness. It is no suprise then that after small doses of amphetamine, vigilance is increased. The results obtained in these studies therefore correlate with the clinical observation of the effect of small doses of amphetamine.

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